CORRECTED VERSION*

PCT

209/250

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:
A61K 7/00	A1	WO 96/19184
		(43) International Publication Date: 27 June 1996 (27.06.96)

(21) International Application Number: PCT/US95/16985

(22) International Filing Date: 21 December 1995 (21.12.95)

(30) Priority Data:
08/362,100 21 December 1994 (21.12.94) US

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(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: FORMULATIONS AND METHODS FOR REDUCING SKIN IRRITATION

(57) Abstract

Compositions and methods are provided for inhibiting skin irritation attributable to chemical irritants or environmental conditions, by the application of an anti-irritant amount of aqueous-soluble divalent strontium cation.

* (Referred to in PCT Gazette No.38/1996, Section II)

FORMULATIONS AND METHODS FOR REDUCING SKIN IRRITATION

Technical Field

This invention relates to compositions and formulations, and methods for using the same, to inhibit skin irritation in animals.

Background

Many substances are applied topically to the skin or mucous membranes of humans or animals (hereafter "skin") in order to alter the subject's appearance, to protect the subject from the environment, or to produce a biological change in the skin or other tissue for therapeutic, preventive or cosmetic purposes. These substances may generically be termed "topical products" and include such topically applied substances as cosmetics, over-the-counter and prescription topical drugs, and a variety of other products such as soaps and detergents.

Topical products occur in a variety of forms, including solids, liquids, suspensions, semisolids (such as creams, gels, pastes or "sticks"), powders or finely dispersed liquids such as sprays or mists. Examples of topical products commonly classified as "cosmetics" include skin care products such as creams, lotions, moisturizers and "treatment cosmetics" such as exfoliants and/or skin cell renewal agents; fragrances such as perfumes and colognes, and deodorants; shaving-related products such as creams, "bracers" and aftershaves; depilatories and other hair removal products; skin cleansers, toners and astringents; pre-moistened wipes and washcloths; tanning lotions; bath products such as oils; eye care products such as eye lotions and makeup removers; foot care products such as powders and sprays; skin colorant and make-up products such as foundations, blushes, rouges, eye shadows and liners, lip colors and mascaras; lip balms and sticks; hair care and treatment products such as shampoos, conditioners, colorants, dyes, bleaches, straighteners, and permanent wave products; baby

immune system directed toward the chemicals alone or in combination with skin components (e.g. antigens).

The sensation of itch is one of the most common skin problems experienced by humans and animals. Itch can be defined as a sensation which provokes the desire to scratch the site from which the sensation originates. All skin contains sensory nerves which can transmit itch or other sensory impulses in response to chemical irritation, environmental exposure or disease processes. Although the precise population of itch producing nerves have not been identified, the thinnest, unmyelinated nerve population, termed type C nociceptive neurons are thought to be the most important in producing the sensation. Itch: Mechanisms and Management of Pruritus. Jeffrey D. Bernhard. McGraw-Hill, Inc. (San Francisco, 1994), pp. 1-22. The sensory nerves of the skin can be considered to be a "final common pathway" for the many irritating conditions which may be ultimately sensed as itch including chemical exposure, environmental exposure (such as that which produces dry, itchy skin) and disease processes such as atopic dermatitis. Many chemical substances are able to produce itch or other sensory impulses when topically applied to the skin. No matter what the ultimate cause of itch, the sensation experienced is the same and provokes the desire to scratch.

Many ingredients used in topical products are known irritants or are potentially irritating, especially to people with "sensitive skin". These irritating ingredients include fragrances, preservatives, solvents, propellants and many other ingredients that might otherwise be considered inert components of the products. Additionally, many topical product active ingredients, including chemicals that may also be classified as drugs, produce irritation when applied to the skin. These include, but are not limited to, such ingredients as exfoliants and skin cell renewal agents, anti-acne drugs, antiperspirant compounds, antihistamines, anti-inflammatory agents, skin protective agents, insect repellent

can greatly increase irritation from topically-applied products. A very common condition due to low humidity is termed "winter itch" in which the very low humidity characteristics of many cold climates (particularly when accompanied by indoor heating) or long exposure to refrigerated air from air conditioners in the summer produces itchy skin -- especially in older people -- which can exacerbate the irritating effects of topical products. Additionally, soaps, detergents, cleansing products, shaving creams, alcohol and other products which remove some of the skin's protective lipids and/or secretions may increase the skin's permeability and sensitivity to topically-applied chemicals which would otherwise not produce irritation. Normal processes such as sweating may also increase the ability of irritant materials, such as antiperspirants, deodorants or sunscreens, to penetrate the skin through pores or glands, thus exacerbating the potential for irritation. Exposure of the skin to high humidity environments or liquids may also increase the ability of potential irritants to penetrate the skin. Similarly, the skin may become sensitized or inflamed due to infection, shaving abrasion, repeated or excessive washing or bathing, sun exposure, or other mechanical abrasion or injury, resulting in sensory irritation responses upon subsequent application of underarm deodorants, after-shaves or other topical products.

In addition to chemical and environmental causes of skin irritation, many people have an inherent sensitivity or genetic predisposition to skin irritants. People with respiratory allergies, for example, tend to have excessively dry skin which facilitates increased absorption of potentially irritating chemicals. The excessively dry skin which accompanies atopic dermatitis, for example, predisposes patients with this condition to irritation from many topically-applied products. Other skin diseases and conditions such as allergic or non-allergic contact dermatitis, asthma (including exercise-induced asthma as may be precipitated by inhalation of cold or dry air), rhinitis, conjunctivitis,

skin wrinkles, particularly facial wrinkles, or as anti-acne, anti-"dry skin" or skin whitening agents. See U.S. Patent Nos. 4,105,782, 4,105,783, 4,246,261, and 5,091,171 (Yu et al.) and 5,262,153 (Mishima et al.); W.P. Smith, "Hydroxy Acids and Skin Aging," Soap/Cosmetics/Chemical Specialties for September 1993, p. 54 (1993). Hydroxy acids, in concentrations high enough to exfoliate, are well known often to cause skin irritation and rashes. The danger of irritation is even higher for persons that have sensitive skin.

Currently available methods reported by Yu et al. to reduce the irritation caused by hydroxy- and keto-acids in topical products include adding a strong alkali metal base such as sodium hydroxide or potassium hydroxide, thereby raising the pH of the preparation and reducing the acidity of the hydroxy acid. Such methods have the reported drawback of reducing the ability of the resulting hydroxy acid salt to penetrate the skin and thus compromising the beneficial effects (particularly anti-acne or anti-"dry skin" effects) of the hydroxy acid. Alternatively, Yu et al. have proposed the approach of formulating the hydroxy acid with a non-alkali metal base such as ammonium hydroxide or an organic base such as a primary, secondary or tertiary organic amine, thereby forming an amide or ammonium salt of the active ingredient hydroxy (or keto) acid. See U.S. Patent Nos. 4,105,782 and 4,105,783 (Yu et al.). The effect of such formulations is, again, to raise the pH of preparation to a non-irritating level. However, the increased pH (reduced acidity) of the resulting preparations renders them less efficacious as exfoliating or anti-wrinkle agents, which desirably have an acidity equivalent to pH 1-6, and more preferably pH 2-4. See Smith, above, at Table 1. Other approaches to reducing the irritation associated with exfoliant products include the use of slow-release topical formulations such as polymer-based vehicles (see, e.g., Chess et al., U.S. Patent No. 4,971,800) or microsponges, and inclusion of, e.g., plant-derived anti-irritant components (see, e.g., Smith et al., U.S. Patent No. 5,028,428).

ion channel or pump operation or by altering the transmembranal action potential, or the cation may interfere with the transmission of nerve impulses from one nerve cell to another (as by suppressing neurotransmitter release). General descriptions of the function of channel proteins are given in B. Hille (ed.), Ionic Channels of Excitable Membranes, Sinauer Associates (Sunderland, Mass.: 2d Ed. 1992), and Siemen & Hescheler (eds.), Nonselective Cation Channels: Pharmacology, Physiology and Biophysics, Birkhauser Velgag (Basel, Switzerland: 1993). In addition, or alternatively, the strontium cation may act to inhibit or modify the action of skin cell proteases or other irritation-inducing biological molecules (such as eicosanoids or cytokines) that may otherwise be activated by topical application of skin irritants, or may alter "second-messenger" function within sensory cells.

A number of ionic species, and certain metal cations in particular, have been associated with various aspects of nerve cell activity. For example, during the resting (polarized) state of a typical nerve cell, the intracellular concentration of potassium in the nerve axon is high relative to the extracellular potassium concentration, and the intracellular concentration of sodium is low relative to the extracellular sodium concentration. During the process of nerve depolarization, potassium ions flow out of the cell across the membrane, and sodium ions flow into the cell, through pores created by axonal membrane proteins known as "channels". Following depolarization, membranal proteins known as ion "pumps" act to reestablish the resting, polarized state of the cell.

Other metal ions have also been shown to influence nerve function. For example, calcium (Ca^{2+}) is carefully regulated in higher eukaryotic organisms and is reported to have many important effects on cellular and neuronal activity. Calcium signaling pathways control many cellular processes, including fertilization, cell growth, transformation, secretion, smooth muscle contraction, sensory perception and neuronal signaling (Berridge, Nature 361(6410), 315-25

alter the activity of various nerve cell enzymes. Harris et al., J. Pharmacol. Exp. Therap. 195, 488-498 (1975).

Calcium, strontium, barium and certain other divalent cations have also been reported to modulate or block the gating and/or conductance properties of certain ion transporting proteins such as sodium and potassium channels (Shioya et al., Pflugers Arch. 422, 427-435 (1993); Cukierman, Biophys. J. 65, 1168-73 (1993); Marrero & Orkland, Proc. R. Soc. Lond. B. 253, 219-224 (1993)). One mechanism that has been proposed to explain these effects is that the cations may bind to the outer membrane of the nerve cell, thus altering the electric field locally near the membrane (Stein, above, at p. 57); others have proposed models involving specific interactions between the divalent cations and the channel gate and/or pore (Shioya et al., above; Cukierman, above). Alternatively, the cations may regulate the function of many calcium-binding regulatory proteins such as calmodulin or may affect intracellular second messengers such as cyclic nucleotides ("Calcium: Controls and Triggers," in daSilva & Williams (eds.), The Biological Chemistry of the Elements: The Inorganic Chemistry of Life, Oxford University Press (New York: 1991), pp. 268-98).

Early studies involving selected nerve cell samples indicated that certain divalent cations, including magnesium and calcium, can have a "depressant" effect on nerve activity (Frankenhaueser & Meves, J. Physiol. 142, 360-365 (1958); Krnjevic, Brit. Med. Bull. 21, 10 (1965); Kato & Somjen, J. Neurobiol. 2, 181-195 (1969); Kelly et al., J. Neurobiol. 2, 197-208 (1969)). These results were generally attributed to post-synaptic membranal effects, as for example the inhibition of potassium or sodium currents in nerve samples exposed to the cations.

While laboratory studies such as these using cultured single cells or microelectrode single-cell electrophysiological techniques have done much to advance the understanding of nerve activity, distinct challenges are presented in

In addition, the mechanisms underlying sensory stimulation and perception in the animal body are diverse and exceedingly complex. Even within a single tissue or organ, different nerve groups having different organizations and functions may appear. Depending on how they are disposed within the tissue, the various nerve groups may be differently affected (or affected not at all) by an applied agent. Moreover, to the extent that different types of nerve cells occur within a tissue, they may have different susceptibilities to a particular applied agent. This is particularly true in the skin, which has nerves adapted to sense a wide variety of sensory inputs.

Another complicating factor arises from the detailed nature of nerve cell activity and response. The firing activity of an individual nerve cell may be influenced in a complex fashion, and may vary over time, depending on such factors as the extracellular and intracellular concentration of nerve-related ions as sodium, potassium, chloride, calcium and the like, as well as the time course of exposure to such ions. Other bioactive agents, such as prostaglandins present during inflammatory responses, may further influence nerve sensitivity. In addition, nerves may respond to non-chemical stimuli such as hydrodynamic pressure changes, which in turn may depend on the nature of the tissue in which the nerve is disposed. Such factors lead to considerable clinical uncertainty as to how various agents may affect nervous responses such as pain responses.

For example, studies have been undertaken over the last several decades in an effort to identify and elucidate the effects of various putative tooth-desensitizing agents and therapies. Tooth nerves are disposed primarily in the central pulp of the tooth, but also extend partially into the surrounding "dentin" material. The dentin material is a mineralized collagen matrix containing microscopic, fluid-filled "dentinal tubules." It has long been known that tooth nerve activity (which is sensed as pain) may be triggered by hydrodynamic pressure changes in the tubule fluid, as may be caused for example by probing

(obtained, for example, by deeply abrading the dentin material) have indicated that various divalent cations (particularly calcium and magnesium) may suppress nerve electrical responses, while monovalent potassium evokes a transient electrical response followed by inhibition of excitability (Markowitz & Kim, above; Orchardson, above). In the final analysis, the Markowitz and Kim group concluded that it is difficult to explain the clinical desensitizing effects of the available ionic desensitizing dentrifices (which require several weeks of treatment) in terms of a direct nerve cell membrane function, and that studies undertaken with exposed nerves may not reflect the pain-induction mechanisms observed clinically (Markowitz & Kim, above).

The human skin presents a sensory and structural environment that is much more complicated than that of the tooth. For example, the skin contains nerves and highly specific sensory organs that are specialized and disposed so as to differentiate the stimuli leading to such distinct sensations as heat, cold, pressure, pain, itch and the like. In addition to normal sensory stimuli, nerves in the skin are also responsive to native or foreign chemicals such as proteases, prostaglandins, complement-system molecules, allergens, mitogens and the like which may be presented due to tissue injury or environmental exposure. Agents which are effective to combat one source of sensory stimulus -- for example steroidal agents to treat skin inflammation -- are ineffective against other sensory stimuli such as pressure, heat, or the transitory sting or itch caused by an applied skin care product. Conversely, local anesthetic agents which are effective to depress all sensory or even motor activity in a treated region are not desirable if only a single sensation -- for example a transitory sting or itch -- is sought to be eliminated. To complicate the situation, the structural matrix of the epidermal skin affords a "barrier function" which tends to exclude or inhibit the entry of foreign material, including potentially therapeutic agents.

Preferred embodiments of the present invention utilize an anti-irritant amount of the strontium cation accompanied (as in the form of a salt) by one or more ionizing anionic species, preferably an acidic anion species such as a chloride, nitrate, sulfate, acetate, gluconate or oxalate anion, dissolved or dispersed in an appropriate vehicle. Investigations relating to the present invention have shown that the anti-irritant effects of the cations of the invention can be optimized by suitable selection of the accompanying anionic species. Especially preferred cation-anion pairs include strontium chloride, strontium nitrate, and strontium acetate.

In the preferred embodiments, the cation of the invention is included in a suitable topical vehicle at a concentration of about 10 to about 3000 mM, more preferably about 50 to about 2000 mM, and most preferably about 100 to about 1000 mM. The most highly preferred concentration range in many instances is from about 250 to about 500 mM, as for example where the formulation of the invention includes an irritant ingredient such as an exfoliant ingredient. The appropriate cation concentration can be achieved, for example, using a single strontium salt, or multiple different cation salts may be combined to yield the total desired cation concentration.

In another preferred embodiment, the strontium cation of the invention is combined in a topical product formulation further comprising a potentially irritating ingredient, the cation being present in a total amount effective to reduce or eliminate irritation due to the irritant ingredient.

In another preferred embodiment, the cation of the invention is paired with one or more anionic species selected so as to achieve a desired level of acidity or basicity in the formulated composition, and a total cation concentration effective to reduce skin irritation. In one such particularly preferred embodiment, strontium is combined in a hydroxy acid or other exfoliant preparation accompanied by one or more suitable anionic species such that the

Description of the Drawings

FIGURES 1 through 4 depict experimental data showing the time course of irritation responses (FIG. 1), the cumulative irritation over time (FIG. 2), and the subject-by-subject cumulative irritation suppression and irritation responses (FIGS. 3 and 4) for a panel of humans treated with 250 mM strontium nitrate (and control) in a lactic acid skin irritation challenge.

FIGURES 5 through 8 depict experimental data showing the time course of irritation responses (FIG. 5), the cumulative irritation over time (FIG. 6), and the subject-by-subject cumulative irritation suppression and irritation responses (FIGS. 7 and 8) for a panel of humans treated with 250 mM strontium nitrate (and control) in a capsaicin skin irritation challenge.

FIGURES 9 through 12 depict experimental data showing the time course of irritation responses (FIG. 9), the cumulative irritation over time (FIG. 10), and the subject-by-subject cumulative irritation suppression and irritation responses (FIGS. 11 and 12) for a panel of humans treated with 250 mM strontium nitrate (and control) in a glycolic acid skin irritation challenge.

FIGURES 13 through 16 depict experimental data showing the time course of irritation differential responses (FIG. 13), the cumulative irritation differential over time (FIG. 14), and the subject-by-subject cumulative suppression of irritation differential and irritation differential responses (FIGS. 15 and 16) for a panel of humans treated with 250 mM strontium nitrate (and control) in a benzoyl peroxide skin irritation challenge.

FIGURES 17 through 20 depict experimental data showing the time course of irritation responses (FIG. 17), the cumulative irritation over time (FIG. 18), and the subject-by-subject cumulative irritation suppression and irritation responses (FIGS. 19 and 20) for a panel of humans treated with 500 mM strontium nitrate (and control) in a post-shaving ocean water skin irritation challenge.

acid, tartaric acid, mandelic acid, benzylic acid, and gluconic acid), as well as in certain prescription topical drugs containing high (for example, 12% w/w or even higher) dosage forms of such irritants. The irritation attributable to combinations of such irritating ingredients, such as lactic acid/salicylic acid combinations and hydroxy acid/retinoid combinations, as well as irritation attributable to purified isomeric forms of such ingredients, can also be inhibited by the formulations of the invention. Additionally, formulations containing the cation are useful in ameliorating irritation in conditions where the skin is inherently hypersensitive to topical products (e.g. dry skin, "winter itch," and other inflammation or injury conditions) and in ameliorating the irritation due to such conditions even in the absence of other applied topical products. The formulations are also useful in treating non-human animal skin irritation, as for example dog or cat irritation and resultant scratching due to fleas or other skin disease or condition.

An additional benefit of the present anti-irritant compounds and formulations is that they do not have the undesirable anesthetic side-effects exhibited by Lidocaine and other similar skin local anesthetics. Upon application of a solution of the compound used in the clinical trials described here, subjects typically reported no sensations other than those sensations caused by the vehicle alone, and no lack of normal sensations.

Formulations of the Invention

The anti-irritant topical formulations of the invention comprise a topical vehicle suitable for administration to the animal (particularly human) skin, and an amount of the strontium cation effective to reduce, inhibit or eliminate existing or potential skin irritation. The cation component is, of course, accompanied in the formulation by one or more charge-neutralizing anionic counterions, although the cation-anion pairs as originally incorporated into the vehicle may become dissociated in the resulting formulation, or the strontium

10 mM:	0.21% (w/v)	0.23% (w/w)
50 mM:	1.05% (w/v)	1.14% (w/w)
100 mM:	2.1% (w/v)	2.28% (w/w)
250 mM:	5.3% (w/v)	5.7% (w/w)
500 mM:	10.5% (w/v)	11.4% (w/w)
1000 mM:	21.2% (w/v)	22.8% (w/w)
1500 mM:	31.7% (w/v)	34.2% (w/w)

The preferred concentration ranges expressed above contemplate that a typical topical dosage will be approximately 0.5 grams of cation formulation over a 5 cm x 5 cm area of skin (25 cm^2). Clinical studies have shown that such preferred concentration ranges are generally effective to inhibit skin irritation and, in typical topical vehicles, are readily formulated and do not leave any significant visible residue when applied to the skin. Higher concentration formulations, such as saturated pastes or other forms, may also be successfully used, particularly where visible appearance is not a limiting consideration (as in therapeutic applications).

Furthermore, routine clinical assessments such as those described below can readily be employed to optimize the cation concentration and to ascertain if lower, or higher, concentrations are appropriate for a given formulation or irritation indication. For example, the concentration of cation may be adjusted to account for the amount of formulation that is typically applied to a given skin area by the user, which will depend to an extent on the physical nature of the topical vehicle (e.g., lotion as compared to liquid spray vehicles). Likewise, the amount of cation required may be reduced in such cases where the formulation contains a skin penetration-enhancing ingredient or other agent which increases the ability of the cations to permeate the stratum corneum to their site of anti-irritant activity. Preferably, the formulations of the invention include an amount of anti-irritant cation capable of inhibiting irritation in susceptible individuals by

incorporated into the formulations of the invention in order further to inhibit irritation effects or symptoms.

The cation component of the invention is typically incorporated into the present formulations by mixing an appropriate amount of a suitable salt form of the cation into the chosen formulation vehicle, along with such other skin care components as are desired. From a formulation standpoint, it is preferred that the selected salt be sufficiently soluble in the formulation vehicle as to allow a consistent formulation having the desired physical and topical application characteristics. It will be recognized that, depending on the formulation vehicle chosen, the salt form of the cation of the invention may dissociate within the formulation (and in this case may associate with other anions also present in the formulation), or the salt form may remain substantially associated. It is also highly preferred that the salt (or salts) chosen be sufficiently aqueous-soluble such that, upon application to the skin, the component cations (and corresponding counteranions) can dissociate and be taken up into the water-containing milieu of the skin. In addition, it will be clear that the particular salt ingredient(s) chosen should be topically acceptable and preferably will not themselves be irritating, toxic or otherwise deleterious to the user.

With these considerations in mind, it will be recognized that a variety of topically acceptable strontium/counteranion salt ingredients may be utilized in the present formulations in order to achieve the objectives of the invention. Such salts can be readily identified by those skilled in the art in view of the present disclosure based on known physical (e.g., solubility), pharmacological and toxicological information and, if necessary, by the application of routine experimentation.

Examples of potentially suitable counteranion components for use with the strontium cations of the invention include a variety of mono-, di- and trivalent inorganic and organic anions. Examples of potentially suitable

any event, however, the desired level of acidity in such cases can be achieved by adjusting the formulation with a suitable acid (or base if necessary).

In one such particularly preferred embodiment, the strontium cation component of the present invention is combined in a hydroxy acid or other exfoliant preparation accompanied by one or more suitable anionic or other acidic species such that the pH of the hydroxy acid preparation is maintained in the range of pH 1-6, and more preferably in the range of pH 2-4. It will be understood that, where the formulation employs an anhydrous vehicle, the acidity of the formulation may not be expressible in typical pH terms, but that such acidity will manifest itself upon exposure of the formulation to the skin where water is present both intracellularly and extracellularly.

Suitable topical vehicles for use with the formulations of the invention are well known in the cosmetic and pharmaceutical arts, and include such vehicles (or vehicle components) as water; organic solvents such as alcohols (particularly lower alcohols readily capable of evaporating from the skin such as ethanol), glycols (such as glycerin), aliphatic alcohols (such as lanolin); mixtures of water and organic solvents (such as water and alcohol), and mixtures of organic solvents such as alcohol and glycerin (optionally also with water); lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile) such as cyclomethicone, demethiconol and dimethicone copolyol (Dow Corning); hydrocarbon-based materials such as petrolatum and squalene; anionic, cationic and amphoteric surfactants and soaps; sustained-release vehicles such as microsponges and polymer matrices; stabilizing and suspending agents; emulsifying agents; and other vehicles and vehicle components that are suitable for administration to the skin, as well as mixtures of topical vehicle components as identified above or otherwise known

(England, N.J. 1993). See, for example, Chapter 7, pp. 5-14 (oils and gels); Chapter 8, pp. 15-98 (bases and emulsions); Chapter 9, pp. 101-120 ("all-purpose products"); Chapter 10, pp. 121-184 (cleansing masks, creams, lotions); Chapter 11, pp. 185-208 (foundation, vanishing and day creams); Chapter 12, pp. 209-254 (emollients); Chapter 13, pp. 297-324 (facial treatment products); Chapter 14, pp. 325-380 (hand products); Chapter 15, pp. 381-460 (body and skin creams and lotions); and Chapter 16, pp. 461-484 (baby products); the contents of which are incorporated herein by reference.

The formulations of the invention are most preferably formulated such that the cation component of the formulation (as occurring with any accompanying anion counterion components) is substantially invisible upon application to the skin. This is particularly true in the case of many cosmetic formulations that are applied to the face or other exposed parts of the body, although it is also generally desirable that the cation (and anion) component not be visible even if applied to non-exposed portions of the body. It will be recognized that in some cases, particularly with colored facial skin care products such as blushes, blemish covers, lipsticks and the like, the formulation will be designed to be visible on the skin; in such cases, it is desirable that the cation component itself be "invisible," that is, that it not adversely change the appearance of the overall formulation as applied to the skin.

In this regard, clinical studies relating to the invention have shown that anti-irritant effects can be achieved using cation concentrations well below those concentrations that, as applied in a typical topical vehicle, result in a visible cation (or salt) residue on the skin. For example, a blended formulation of 500 mM strontium nitrate in a silicone-based vehicle (Dow Corning cyclomethicone [DC344] : cyclomethicone/dimethiconol [DC1401] : cyclomethicone/dimethicone polyol [DC3225C] : water; 10:20:15:55) results in

Example 1

Clinical Studies of Anti-Irritation Activity

The objective of the clinical trials was to determine whether and to what extent topical formulations of the strontium cation reduced or prevented skin irritation caused by certain severe skin irritants, including particularly lactic acid and glycolic acid (which are hydroxy acids), capryloyl salicylic acid (a β-hydroxy acid ester) and capsaicin (an isolate from cayenne and paprika known for its skin-irritating properties). The trials were conducted in a double blind, randomized, vehicle-controlled manner. Various formulations of the invention were tested in over 740 people. The results confirm the highly reproducible anti-irritant activity of the formulations of the present invention.

a. Lactic Acid Irritation Trials

1. Protocol

The majority of the trials were conducted using lactic acid as the skin irritant, and proceeded generally as follows.

The subjects were women who had been screened and shown to exhibit normal to above normal susceptibility to irritation by the tested irritant. Tests were conducted in multiple panels of from 7 to 12 subjects each. Subjects were instructed not to wear any makeup or facial lotions to the clinic the day of testing. The subjects were instructed to wash their face with Ivory bar soap in the clinic prior to application of test solutions.

Lactic acid skin-irritant compositions were formulated in an appropriate vehicle prior to application to the skin of the subjects. In the majority of the tests, the irritant composition was 7.5% lactic acid dissolved in a 10% ethanol-in-water solution.

Test anti-irritant formulations containing measured amounts of strontium salts (concentration 250 mM) were applied either (a) 15 minutes prior to

Score	Description of Irritation
0	**NO irritation**
1	**SLIGHT irritation --** (Barely perceptible stinging, burning or itching)
2	**MILD irritation --** (Definite stinging, burning or itching)
3	**MODERATE irritation --** (Distinctly uncomfortable stinging, burning or itching; constantly aware of irritation)
4	**SEVERE irritation --** (Continuous stinging, burning or itching, and intensely uncomfortable; would interfere with daily routine)

Symptom scores were cumulated, separately for the cation-treated and control-treated areas, for each individual and also for the panel as a whole. Individuals not reporting a cumulative score of at least "7" on at least one treatment area were excluded (in a blinded fashion) from further analysis in order to ascertain anti-irritant efficacy with respect to the more severely-susceptible test subjects. From a practical standpoint, scores of "0" and "1" on the above scale would be considered highly desirable for a commercial product because such a response would likely not result in a consumer ceasing to use a product. Some consumers, in fact, might view the "barely perceptible" sensations represented by a score of 1 to be an indication that a facial treatment skin care product (especially an exfoliant) was working as advertised. By contrast, irritation scores of "2", "3" and "4" would likely often result in a consumer never purchasing the product again.

In those subjects and skin samples where an irritation was sensed, the irritation commonly involved a spectrum of burn-sting-itch reactions over time. For example, a subject might at first experience a sting, but moments later might

Pretreatment Tests

Cation	Anion	Salt Formula	Vehicle	Percent Inhibition
Strontium	Chloride	$SrCl_2$	VIS DIFFERENCE	20
Strontium	Nitrate	$Sr(NO_3)_2$	VIS DIFFERENCE	56
Strontium	Acetate	$Sr(CH_3CO_2)_2$	VIS DIFFERENCE	46

Time Zero Tests

Cation	Anion	Salt Formula	Vehicle	Percent Inhibition
Strontium	Chloride	$SrCl_2$	10% EtOH	58
Strontium	Nitrate	$Sr(NO_3)_2$	10% EtOH	64

FIGURES 1 through 4 show more detailed experimental data for one panel test conducted using strontium nitrate (250 mM) as the anti-irritant salt component of the subject formulation (time zero test). FIG. 1 shows the time course of irritation responses for both cation-treated and non-treated (control) skin portions for the panel. FIG. 2 shows the cumulative irritation over time for the same panel, while FIGS. 3 and 4 show cumulative irritation suppression and treated/untreated irritation responses on a subject-by-subject basis. While individual responses vary somewhat, the overall efficacy of the subject formulation is clear.

b. Capsaicin Irritation Trials

Similar clinical trials were conducted to assess the efficacy of the cation of the invention to inhibit irritation induced by capsaicin. The clinical protocol was similar to that conducted with lactic acid, with the irritant/anti-irritant and

c. Glycolic Acid Irritation Trials

Following a protocol parallel to that of the lactic acid irritant trials described above, glycolic acid (6.0% in 10% ethanol-in-water) was applied as a skin irritant to subject panels. Strontium nitrate was co-administered as an anti-irritant (time zero testing), and was shown to inhibit cumulative irritation in subject panels by 64% to 84% at concentrations ranging from 250 mM to 500 mM. Time course and subject-by-subject data for one such test (cation concentration 250 mM) are presented in FIGS. 9 through 12.

d. Benzoyl Peroxide Irritation Trials

In this test, male and female subjects were recruited who had experienced a grade "2" or higher response in the sting/burn/itch lactic acid irritation protocol described above. Test subjects were limited to those who self-reported a sensitivity (sting, burn, itch) to benzoyl peroxide.

Subjects were instructed not to wear makeup or facial lotions on the day of testing. Those who had applied sunscreens to the face within 24 hours prior to testing, or who had taken any oral analgesic within 12 hours prior to testing, were disqualified. Subjects were instructed to wash their face with Ivory bar soap prior to application of test and control solutions. All materials were applied and scored in a double-blind, randomized fashion.

Facial irritation was induced by application of a 10% benzoyl peroxide wash product ("Oxy 10") to one side of the face. The other side of the face was treated with the same irritant composition containing 250 mM strontium nitrate as the test anti-irritant. Inactive ingredients in the benzoyl peroxide product included citric acid, cocamidopropyl betaine, diazolidinyl urea, methylparaben, propylparaben, sodium citrate, sodium cocoyl isethionate, sodium lauroyl sarcosinate, water, and xanthum gum.

preferred because it avoids uncertainty and "carry-over" effects from one side of the face to the other.

FIGURES 13 through 16 depict results obtained in this protocol using strontium nitrate as the anti-irritant cation component (250 mM). FIG. 13 shows the time course of differential irritation responses for both cation-treated and non-treated (control) skin portions for the panel. FIG. 14 shows the cumulative irritation over time for the same panel, while FIGS. 15 and 16 show cumulative irritation suppression and treated/untreated irritation responses on a subject-by-subject basis.

e. Post-Shaving Ocean Water Irritation

Ocean water is known to induce irritation in subjects with sensitive skin, particularly if the skin has been abraded by shaving or other means. The present test was performed to determine the ability of the present cation formulations to inhibit irritation of shaved skin due to ocean water.

Female subjects were instructed not to apply any sunscreen to their legs within 24 hours prior to testing, and not to ingest any oral analgesic medications within 12 hours prior to testing. The subjects were instructed to shave the lateral portions of their calves, spanning from the ankle to below the knee, with Ivory soap and a disposable razor prior to application of test, control and ocean water irritant solutions. All materials were applied and scored in a double-blind, randomized fashion.

Following shaving, 1 ml of pretreatment solution (test or control) was applied from coded vials to the respective right and left calves using cosmetic sponges. The test cation solution contained strontium nitrate (500 mM) in nanopure water (pH 4.5), and the control vehicle was nanopure water (pH 5.5). The solutions were allowed to dry for 2-3 minutes. Cosmetic sponges saturated with ocean water (La Jolla, California) were used to apply ocean water challenge

both cation-treated and non-treated (control) skin portions for the panel. FIG. 22 shows the cumulative irritation over time for the same panel, while FIGS. 23 and 24 show cumulative irritation suppression and treated/untreated irritation responses on a subject-by-subject basis.

Example 2

Dose-Response Studies

Additional studies of anti-irritant activity using varying concentrations of strontium cations were conducted in order to assess the dose-response behavior of the present formulations. The lactic acid irritation protocol described above was used, in which the anti-irritant cation component was strontium nitrate (31-500 mM). Cumulative irritation inhibition data are set forth in the following table, and are depicted graphically in FIG. 25.

Concentration (mM)	Percent Inhibition
31	27
62	32
125	42
250	72
500	82

Example 3

Additional Formulation Examples

Cation salts of the invention were formulated at various concentrations in a number of commercially available topical vehicles, and also in various commercially available topical cosmetic products. The resulting mixtures generally did not alter the texture, color, consistency or other physical properties of the product, and could be used as formulations to inhibit topical irritation.

"DC1401"), 15 ml cyclomethicone/dimethicone copolyol (Dow Corning, "DC3225C") and 10 ml glycerin and blended for 2-3 minutes. Imidizolidinyl urea (0.5%) was added as a preservative. A clear, thick gel resulted (100 ml).

b. Commercial Cosmetic Vehicles

Topical solution forms of strontium nitrate, strontium chloride and strontium acetate were prepared by combining various amounts of the named salts with Elizabeth Arden Visible Difference Refining Toner (an alcohol-containing solution). The concentrations achieved were shown to be effective to inhibit skin irritation as described in the protocols set forth above.

Similarly, other solution forms of strontium nitrate were prepared by combining anti-irritant effective amounts of the salt with Estee Lauder Clean Finish Purifying Toner Normal/Dry, Oil of Olay Refreshing Toner Cleanser and Toner, Mary Kay Refining Refreshener Formula 2, Clearasil Clearstick Max Strength, and Oxy-10 Benzoyl Peroxide Wash.

Topical lotion forms of strontium nitrate were prepared by combining anti-irritant effective amounts of the salt with Cheseborough-Ponds Lotions (CCB-3-83-L15), Vaseline Intensive Care Lotion Smooth Legs and Feet, and Lubriderm Moisture Recovery Lotion. Similarly, serum and cream forms of strontium nitrate were prepared by combining anti-irritant effective amounts of the salt with Mary Kay Revival Serum (with 15% lactic acid) and L'Oreal Vichy Novactia Cream (with 2% capryloyl salicylic acid), respectively.

The foregoing examples are not intended to limit the scope of the present invention, which is set forth in the following claims. In particular, various equivalents and substitutions will be recognized by those skilled in the art in view of the foregoing disclosure, and these are contemplated to be within the scope of the invention.

9. The composition of claim 8 wherein said inhibition of skin irritation represents an average reduction in one or more of sting, burn and itch in at least 10% of the susceptible human population upon topical application of said composition, as compared to the level of irritation induced in said at least 10% of the population upon topical application of a control formulation containing said irritant ingredient in a vehicle without said strontium cation.

10. The composition of claim 1 wherein said composition is a cosmetic product.

11. The composition of claim 10 wherein said composition comprises a skin exfoliant, skin peel or skin cell renewal agent.

12. The composition of claim 10 wherein said irritant ingredient is selected from the group consisting of carboxylic acids, keto acids, α-hydroxy acids, β-hydroxy acids, retinoids, peroxides, and organic alcohols.

13. The composition of claim 12 wherein said irritant ingredient comprises lactic acid or a salt thereof.

14. The composition of claim 12 wherein said irritant ingredient comprises glycolic acid or a salt thereof.

15. The composition of claim 12 wherein said irritant ingredient comprises salicylic acid or a salt thereof.

16. The composition of claim 12 wherein said irritant ingredient comprises a combination of lactic acid and salicylic acid, or salts thereof.

17. The composition of claim 12 wherein said irritant ingredient comprises capryloyl salicylic acid or a salt thereof.

18. The composition of claim 12 wherein said irritant ingredient comprises citric acid or a salt thereof.

19. The composition of claim 12 wherein said irritant ingredient is a retinoid selected from tretinoin, retinol, retinal and derivatives thereof.

32. The composition of claim 10 wherein said composition is a hair care or hair treatment product.

33. The composition of claim 32 wherein said composition is selected from the group consisting of shampoo, conditioner, colorant, dye, bleach, permanent wave and hair straightener products.

34. The composition of claim 10 wherein said composition is selected from the group consisting of cleansers, astringents, toners, rinses, serums and masks.

35. The composition of claim 10 wherein said composition is a facial cosmetic product.

36. The composition of claim 10 wherein said composition is selected from the group consisting of creams, lotions and moisturizers.

37. The composition of claim 1 wherein said composition is selected from the group consisting of soaps and detergents.

38. The composition of claim 1 wherein said composition is a topical drug product.

39. The composition of claim 38 wherein said irritant ingredient is capsaicin.

40. The composition of claim 38 wherein said composition is selected from the group consisting of antibiotic, analgesic, contraceptive, anti-acne and anti-dandruff products.

41. The composition of claim 40 wherein said irritant ingredient is benzoyl peroxide.

42. The composition of claim 1 wherein said composition is formulated as a rectal or vaginal suppository, foam, cream, gel, ointment, enema or douche.

43. The composition of claim 1 wherein said composition is formulated for administration to the mouth, throat or lip.

salicylate, ascorbate, formate, succinate, folinate, aspartate, phthalate, oleate, palmitate, stearate, lauryl sulfate, lanolate, myristate, behenate, caseinate, cyclamate, pantothenate, polyaminopolycarboxylates, saccharin, thioglycolate, laurate, methylparaben, propylparaben, ricinoleate and sorbate organic anions.

55. The composition of claim 52 wherein said anion species includes nitrate.

56. The composition of claim 52 wherein said anion species includes sulfate.

57. The composition of claim 52 wherein said anion species includes a halogen selected from chloride and fluoride anions.

58. The composition of claim 1 further comprising at least one second anti-irritant agent.

59. The composition of claim 58 wherein the total amount of said strontium cation and said second agent is capable of inhibiting mean cumulative skin irritation attributable to said irritant ingredient in a susceptible human population by at least about 20%.

60. The composition of claim 58 wherein the total amount of said strontium cation and said second agent is capable of inhibiting by at least about 40% the cumulative skin irritation attributable to said irritant ingredient in at least 10% of the susceptible human population.

61. The composition of claim 58 wherein said second agent is selected from the group consisting of potassium channel mediating, regulating or blocking agents, calcium channel blocking or regulatory agents, sodium channel blocking agents, steroids, non-steroidal anti-inflammatory agents, aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine and other xanthines, and glycyrrhizic acid and its derivatives.

74. The composition of claim 62 wherein said skin irritation is irritation of epidermal skin.

75. The composition of claim 62 wherein said skin irritation is irritation of dermal skin.

76. The composition of claim 67 wherein said skin irritation is attributable to environmental exposure to one or more of sunlight, low humidity, wind, cold temperature, or hot and humid conditions.

77. The composition of claim 67 wherein said skin irritation is attributable to exposure to an irritating chemical agent.

78. The composition of claim 77 wherein said irritating chemical agent exposure is attributable to application of a topical product.

79. The composition of claim 78 wherein said product is selected from the group consisting of antiperspirant, deodorant, sunscreen, tanning, sunburn treatment, insect repellant, exfoliant, skin peel, skin cell renewal, fragrance, shaving or hair removal, hair care or hair treatment, cleanser, astringent, toner, rinse, serum, masks, facial cosmetic, cream, lotion, moisturizer, soap, detergent, and topical drug products.

80. The composition of claim 78 wherein said composition is packaged with instructions directing administration of said composition before, with or following administration of said topical product.

81. The composition of claim 77 wherein said irritating chemical agent exposure is attributable to insect sting or bite, or to plant exposure.

82. The composition of claim 67 wherein said skin irritation is attributable to one or more of shaving, skin cleansing or bathing, sweating, and physical skin trauma.

83. The composition of claim 62 wherein said skin irritation is attributable to dry skin.

consisting of nitrate, sulfate, halogen, carbonate, bicarbonate, hydroxide, oxide, peroxide, nitrite, sulfide, bisulfate, persulfate, glycerophosphate, hypophosphate, borate and titanate inorganic anions, and carboxylic acid, alkoxylate, amino acid, peptide, saturated and unsaturated organic acid, and saturated and unsaturated fatty acid organic anions.

97. The composition of claim 95 wherein said one or more of said counteranions is an organic anion selected from the group consisting of citrate, oxalate, acetate, gluconate, lactate, tartrate, maleate, benzoate, propionate, salicylate, ascorbate, formate, succinate, folinate, aspartate, phthalate, oleate, palmitate, stearate, lauryl sulfate, lanolate, myristate, behenate, caseinate, cyclamate, pantothenate, polyaminopolycarboxylates, saccharin, thioglycolate, laurate, methylparaben, propylparaben, ricinoleate and sorbate organic anions.

98. The composition of claim 62 further comprising at least one second anti-irritant agent.

99. The composition of claim 98 wherein said second agent is selected from the group consisting of potassium channel mediating, regulating or blocking agents, calcium channel blocking or regulatory agents, sodium channel blocking agents, steroids, non-steroidal anti-inflammatory agents, aloe vera, chamomile, α-bisabolol, Cola nitida extract, green tea extract, tea tree oil, licorice extract, allantoin, urea, caffeine and other xanthines, and glycyrrhizic acid and its derivatives.

100. A method for inhibiting skin irritation associated with an irritant ingredient contained in an applied topical formulation, comprising topically administering to an animal subject the composition of claim 1.

101. A method for inhibiting skin irritation in an animal subject comprising topically administering to the subject the composition of claim 62.

114. The method of claim 104 wherein said skin irritation is attributable to one or more of shaving, skin cleansing or bathing, and physical skin trauma.

FIG. 1.

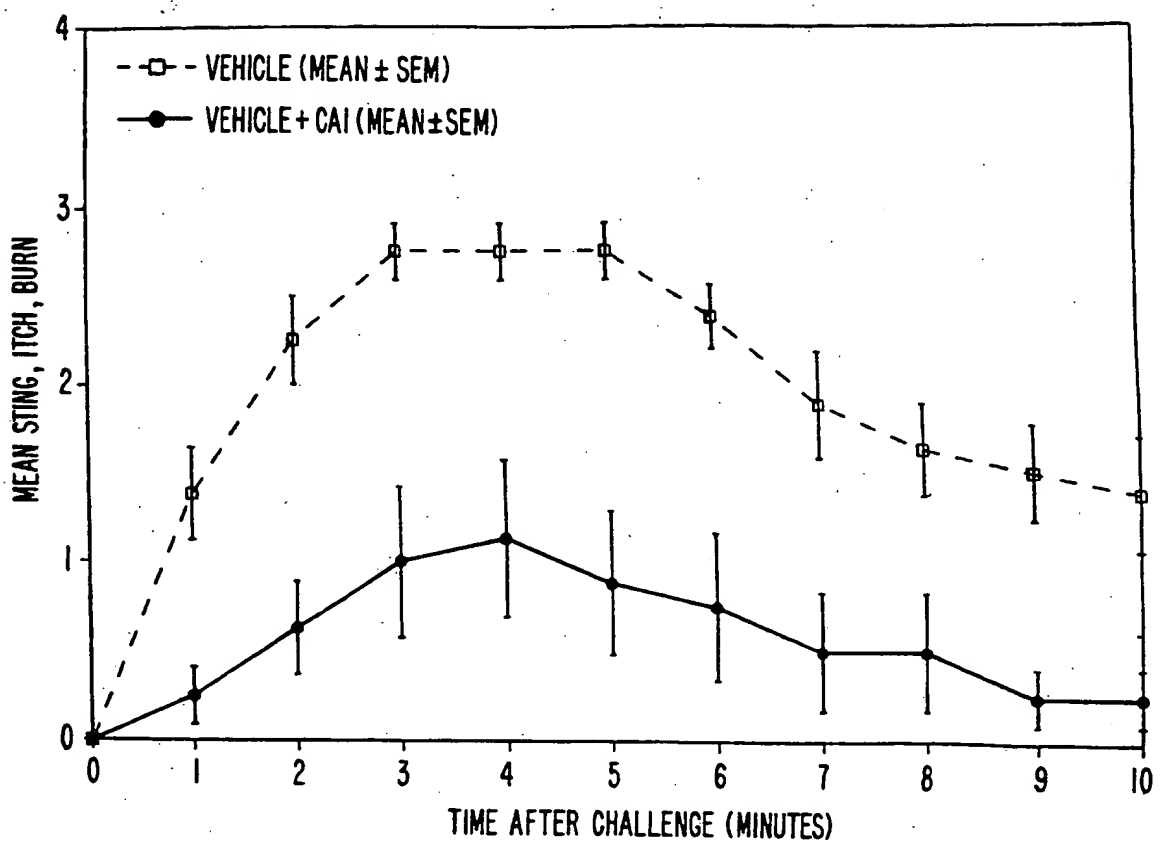

VEHICLE (MEAN ± SEM)
VEHICLE + CAI (MEAN±SEM)
MEAN STING, ITCH, BURN
0
1
2
3
4
0 1 2 3 4 5 6 7 8 9 10
TIME AFTER CHALLENGE (MINUTES)

FIG. 2.

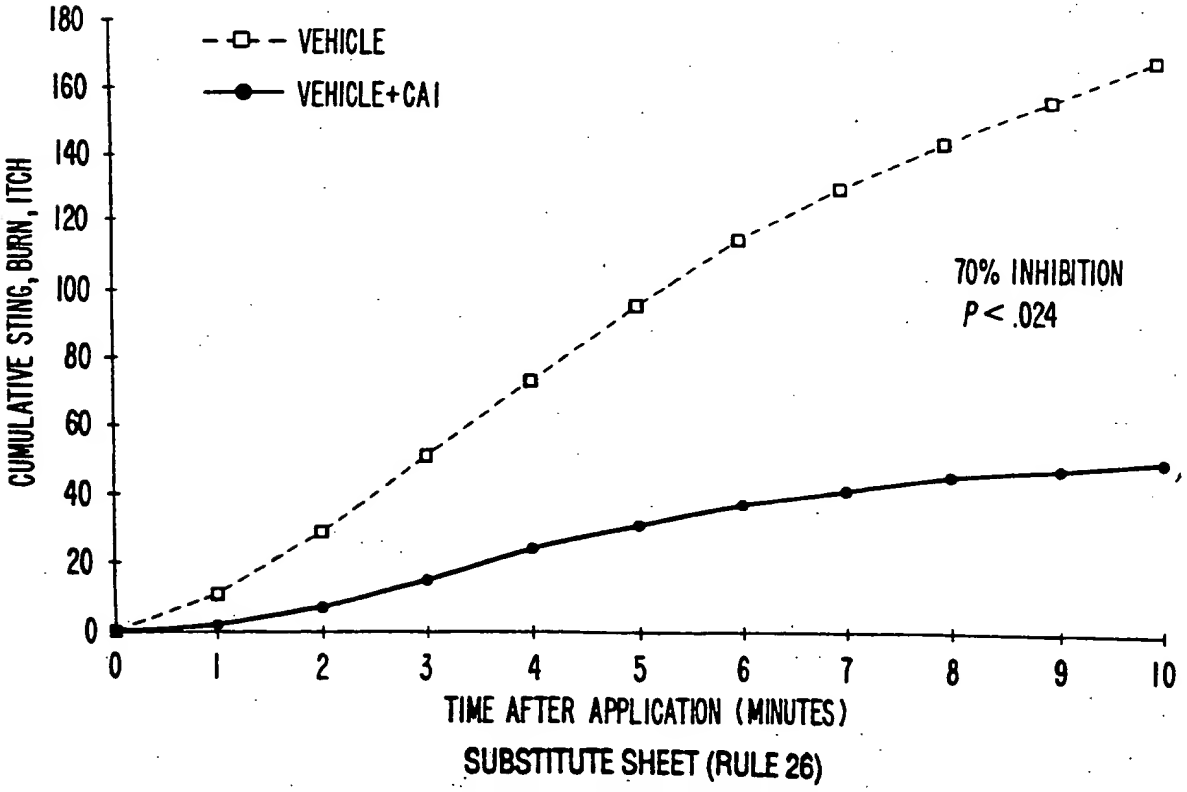

VEHICLE
VEHICLE+CAI
CUMULATIVE STING, BURN, ITCH
0
20
40
60
80
100
120
140
160
180
70% INHIBITION
P < .024
0 1 2 3 4 5 6 7 8 9 10
TIME AFTER APPLICATION (MINUTES)

FIG. 3.

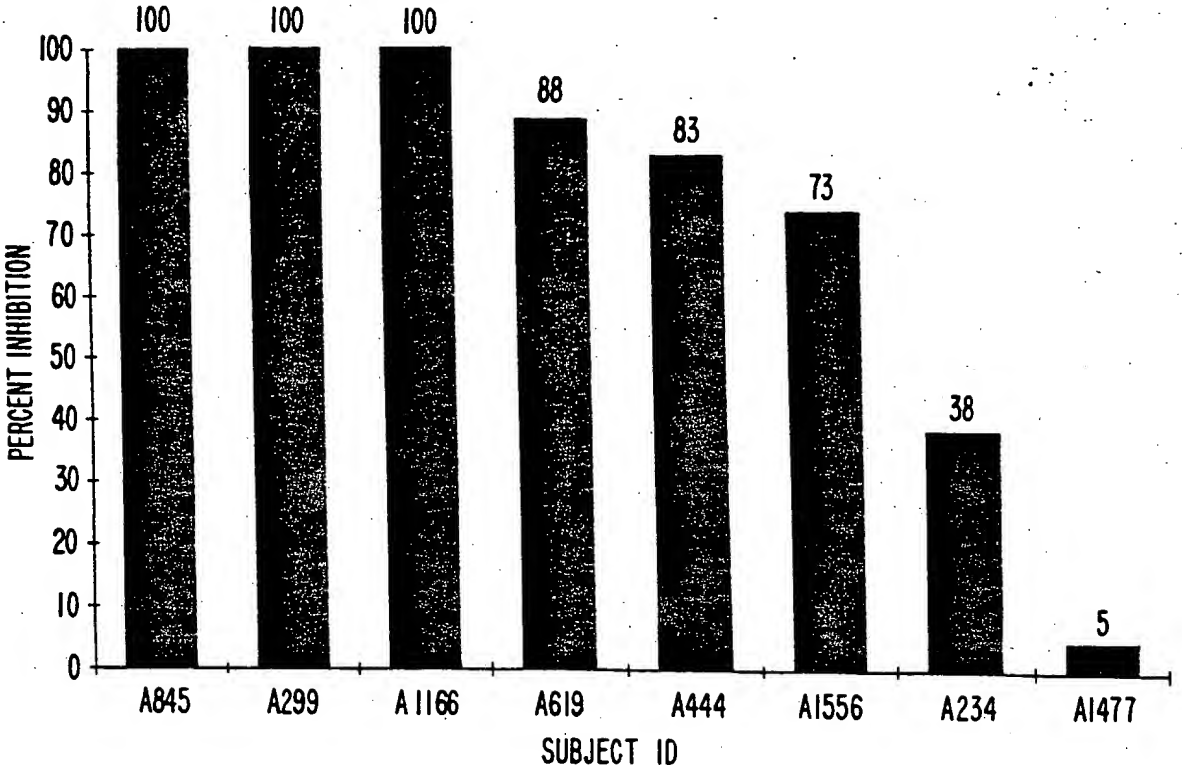

PERCENT INHIBITION
100
90
80
70
60
50
40
30
20
10
0
100
100
100
88
83
73
38
5
A845
A299
A1166
A619
A444
A1556
A234
A1477
SUBJECT ID

FIG. 4.

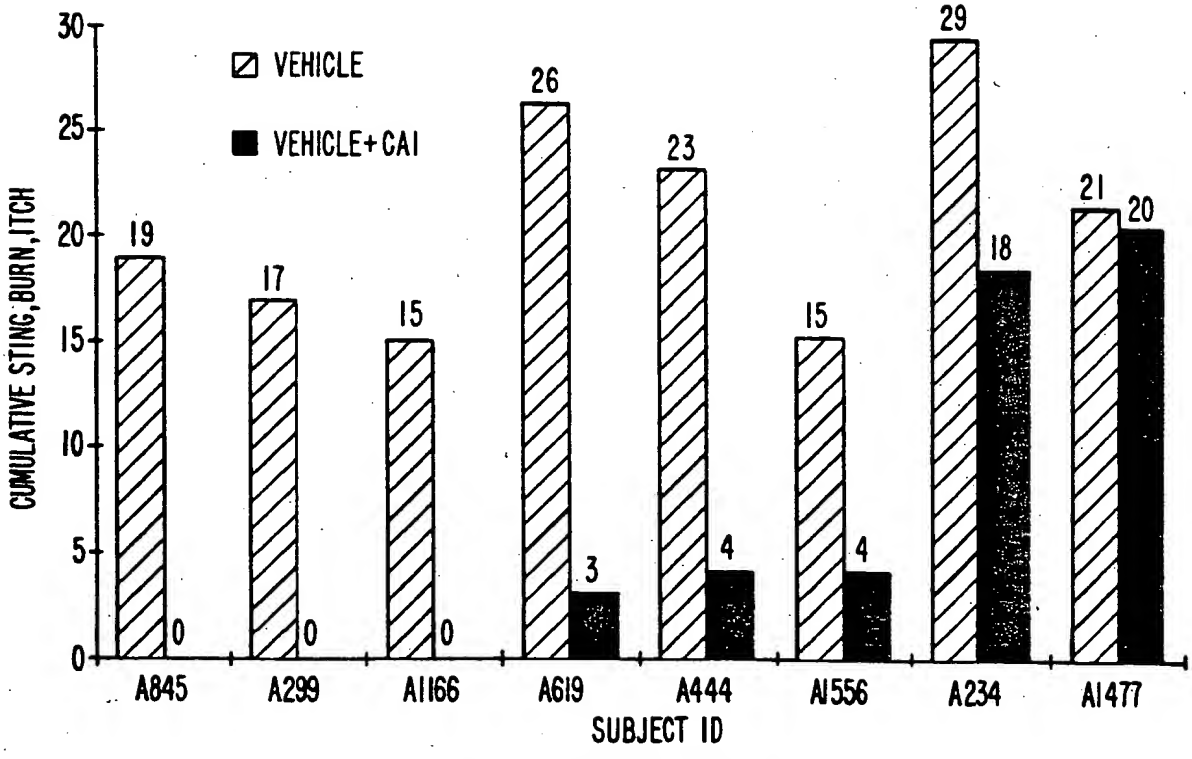

CUMULATIVE STING, BURN, ITCH
30
25
20
15
10
5
0
VEHICLE
VEHICLE+CAI
19
0
17
0
15
0
26
3
23
4
15
4
29
18
21
20
A845
A299
A1166
A619
A444
A1556
A234
A1477
SUBJECT ID

FIG. 5.

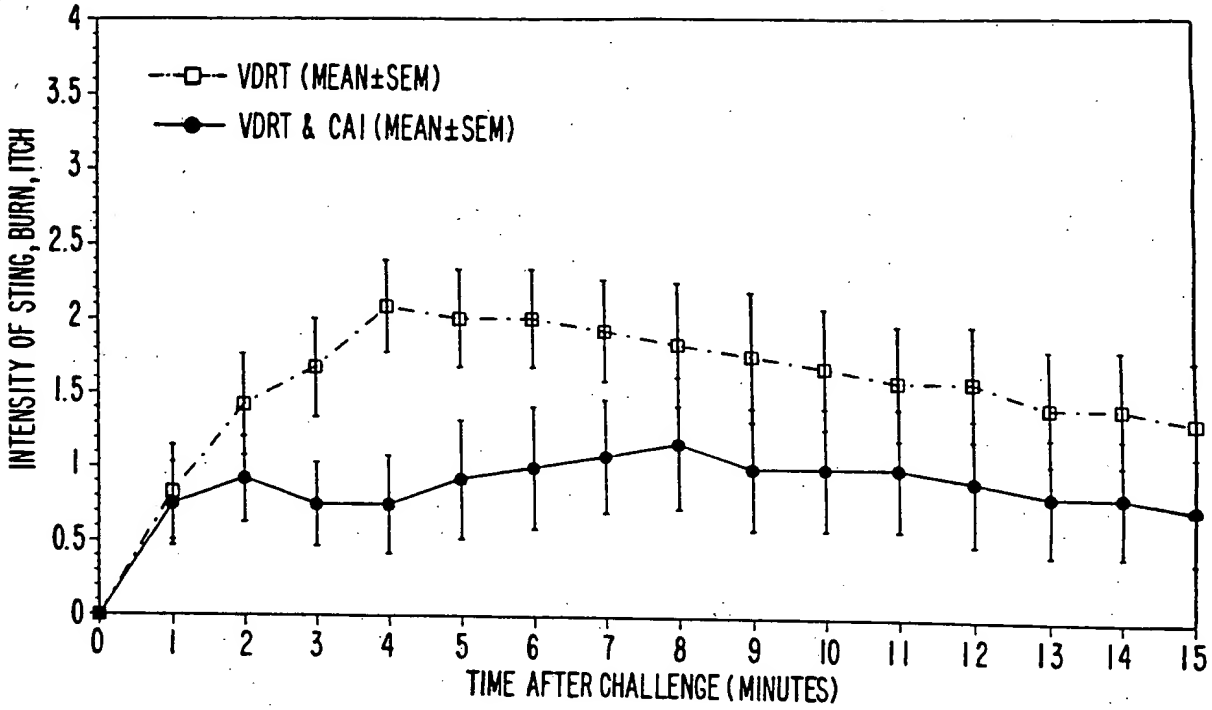

VDRT (MEAN±SEM)
VDRT & CAI (MEAN±SEM)
INTENSITY OF STING, BURN, ITCH
TIME AFTER CHALLENGE (MINUTES)
0
0.5
1
1.5
2
2.5
3
3.5
4
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

FIG. 6.

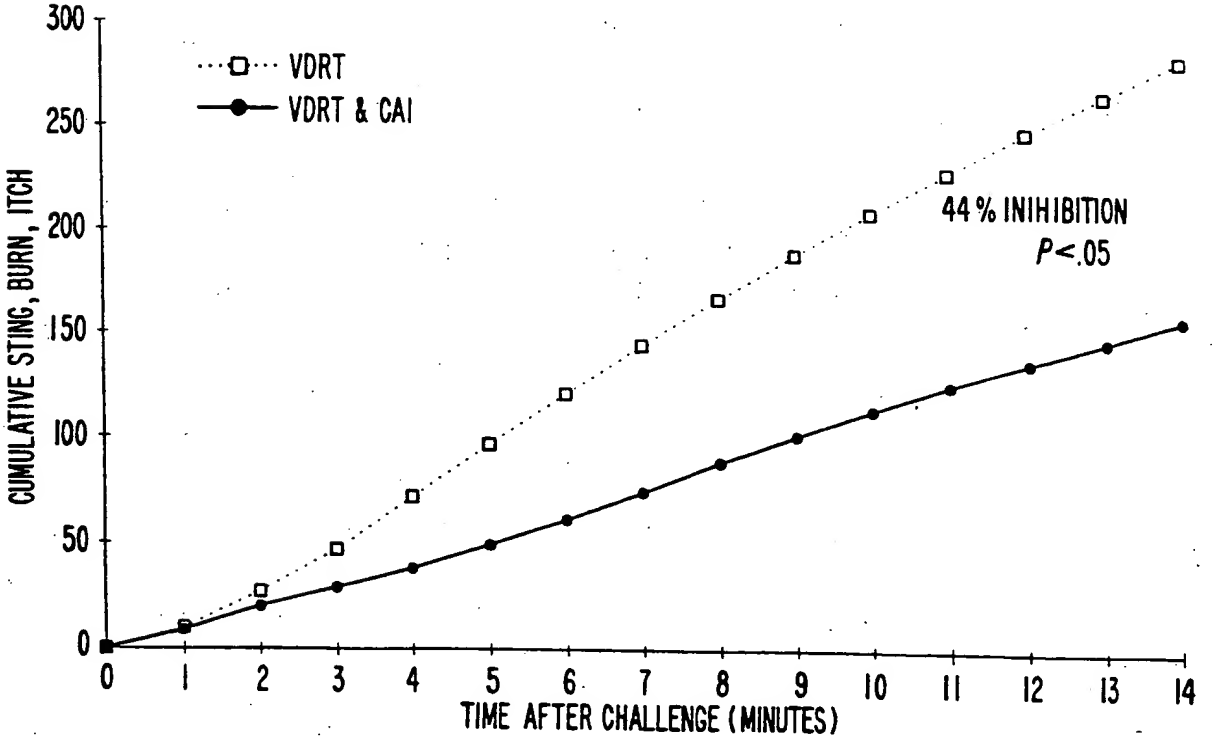

VDRT
VDRT & CAI
44 % INIHIBITION
P<.05
CUMULATIVE STING, BURN, ITCH
TIME AFTER CHALLENGE (MINUTES)
0
50
100
150
200
250
300
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

FIG. 7.

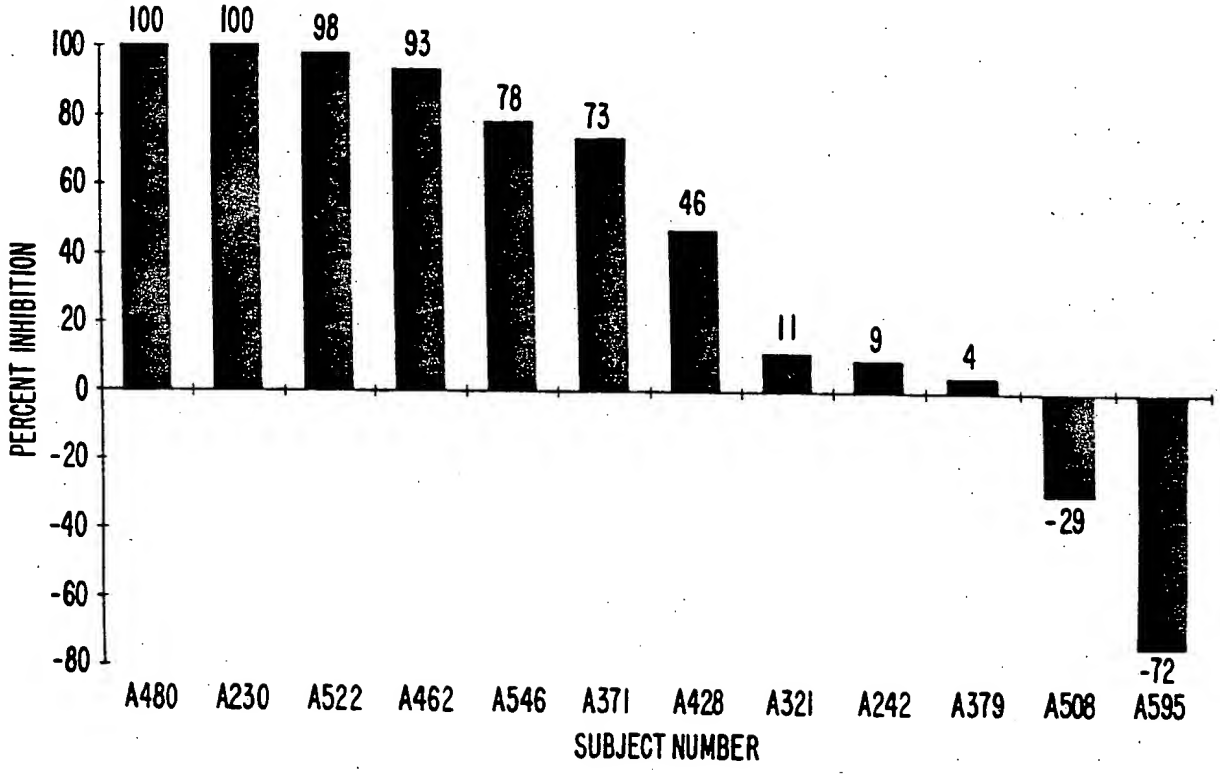

PERCENT INHIBITION
100
80
60
40
20
0
-20
-40
-60
-80
100
100
98
93
78
73
46
11
9
4
-29
-72
A480
A230
A522
A462
A546
A371
A428
A321
A242
A379
A508
A595
SUBJECT NUMBER

FIG. 8.

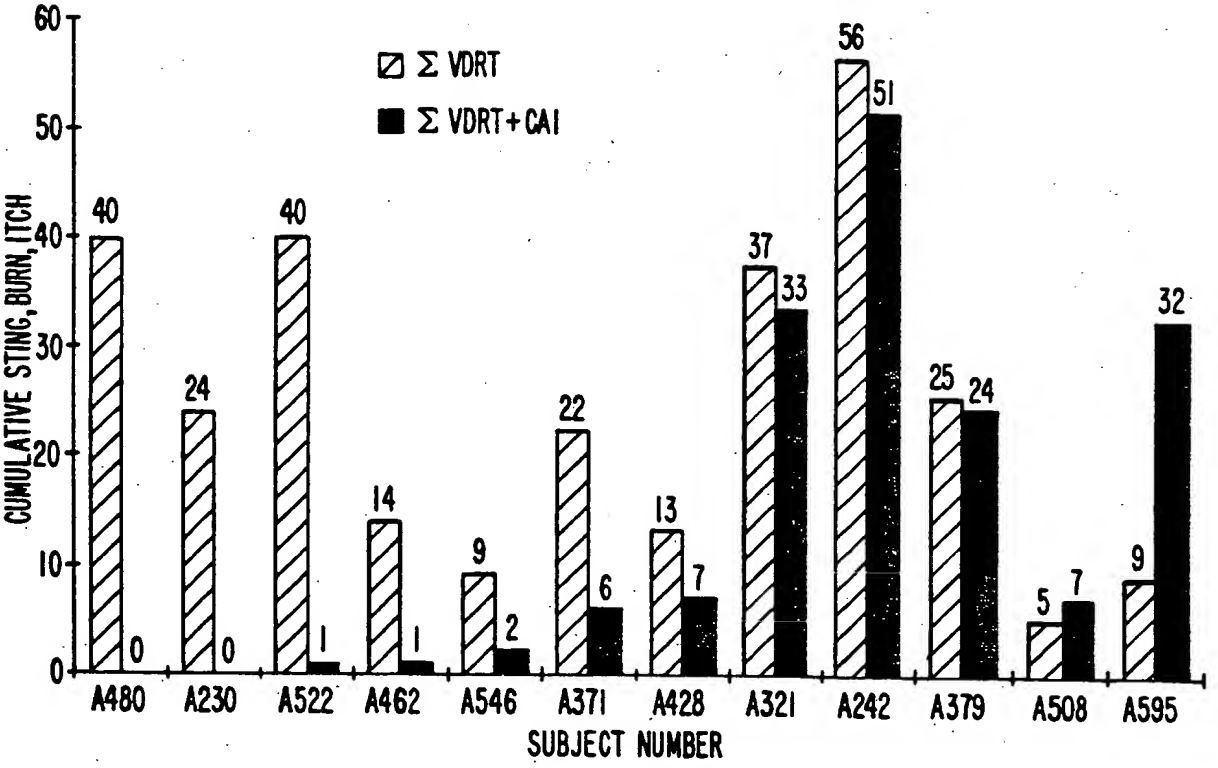

Σ VDRT
Σ VDRT+CAI
CUMULATIVE STING, BURN, ITCH
60
50
40
30
20
10
0
40
0
24
0
40
1
14
1
9
2
22
6
13
7
37
33
56
51
25
24
5
7
9
32
A480
A230
A522
A462
A546
A371
A428
A321
A242
A379
A508
A595
SUBJECT NUMBER

FIG. 9.

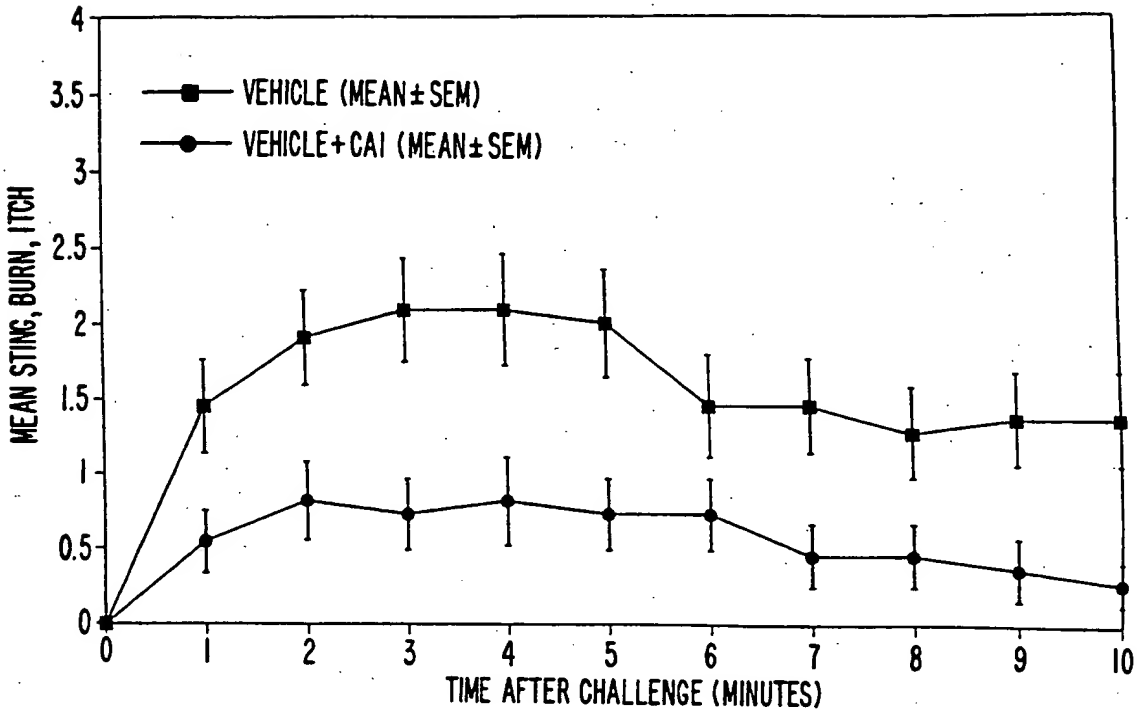

VEHICLE (MEAN ± SEM)
VEHICLE+CAI (MEAN ± SEM)
MEAN STING, BURN, ITCH
TIME AFTER CHALLENGE (MINUTES)
0
0.5
1
1.5
2
2.5
3
3.5
4
0 1 2 3 4 5 6 7 8 9 10

FIG. 10.

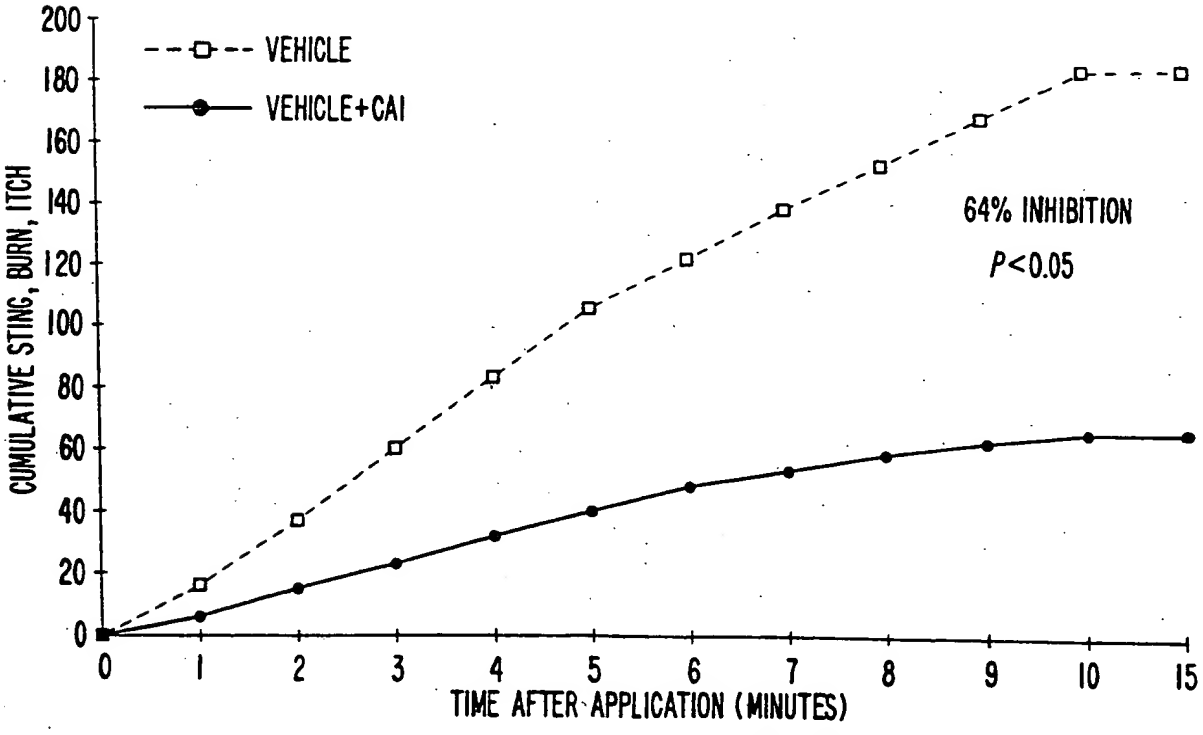

VEHICLE
VEHICLE+CAI
64% INHIBITION
P<0.05
CUMULATIVE STING, BURN, ITCH
TIME AFTER APPLICATION (MINUTES)
0
20
40
60
80
100
120
140
160
180
200
0 1 2 3 4 5 6 7 8 9 10 15

FIG. 11.

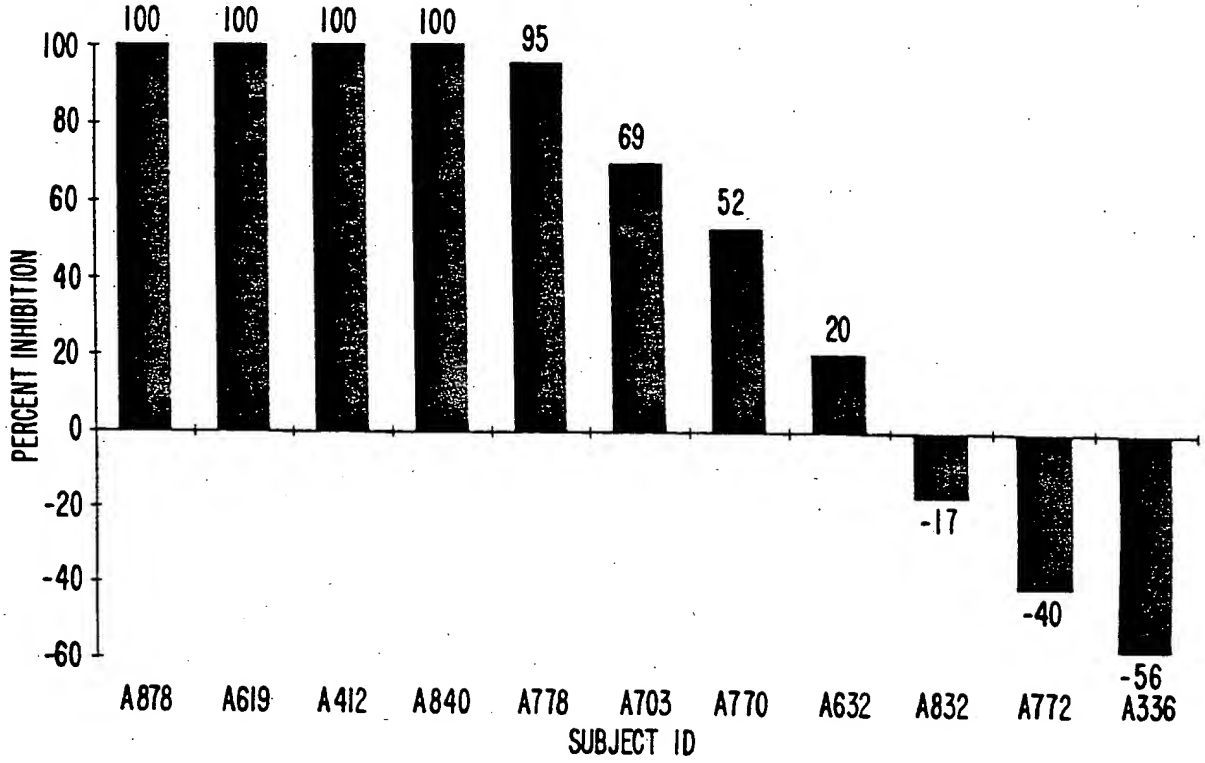

PERCENT INHIBITION
100
80
60
40
20
0
-20
-40
-60
100
100
100
100
95
69
52
20
-17
-40
-56
A878
A619
A412
A840
A778
A703
A770
A632
A832
A772
A336
SUBJECT ID

FIG. 12.

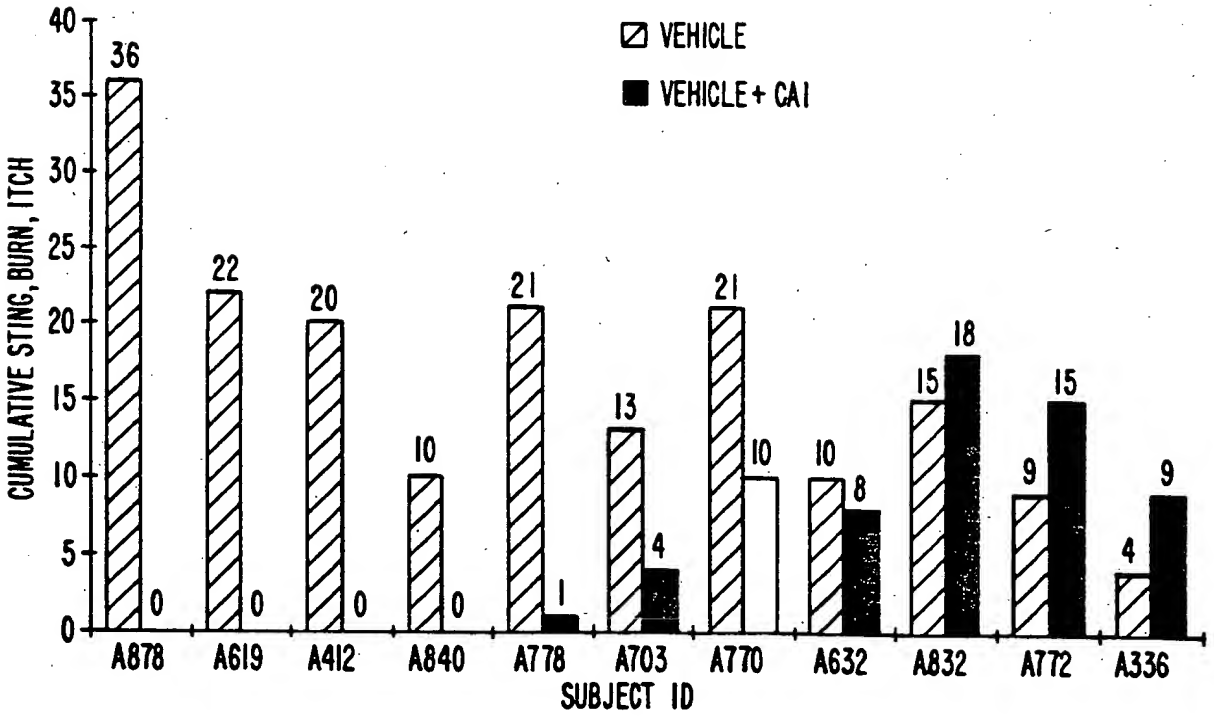

VEHICLE
VEHICLE + CAI
CUMULATIVE STING, BURN, ITCH
40
35
30
25
20
15
10
5
0
36
0
22
0
20
0
10
0
21
1
13
4
21
10
10
8
15
18
9
15
4
9
A878
A619
A412
A840
A778
A703
A770
A632
A832
A772
A336
SUBJECT ID

FIG. 13.

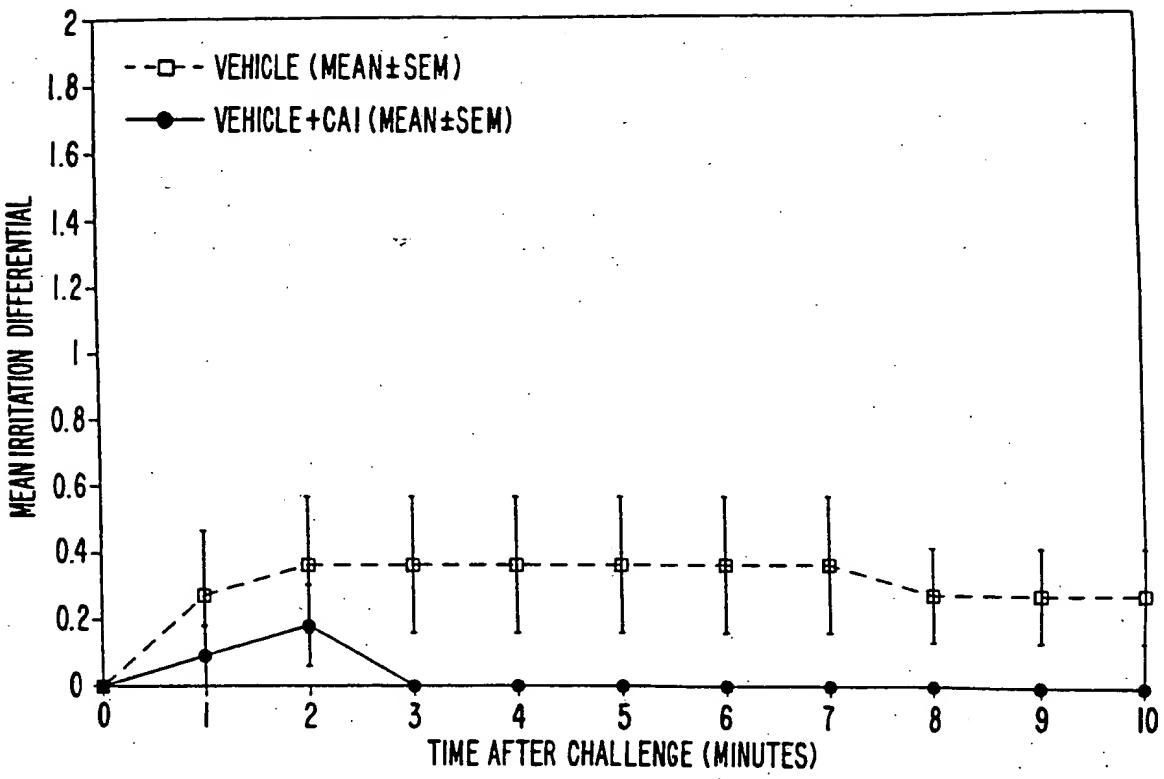

VEHICLE (MEAN±SEM)
VEHICLE+CAI (MEAN±SEM)
MEAN IRRITATION DIFFERENTIAL
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10
TIME AFTER CHALLENGE (MINUTES)

FIG. 14.

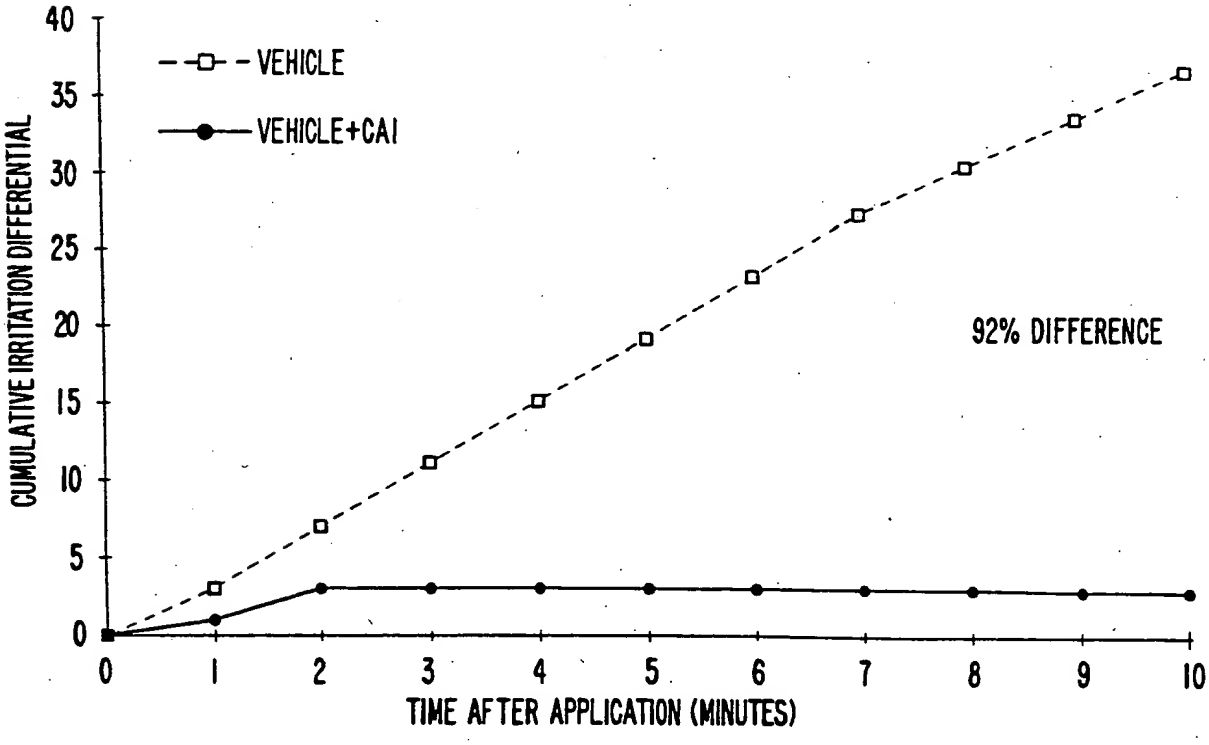

VEHICLE
VEHICLE+CAI
CUMULATIVE IRRITATION DIFFERENTIAL
40
35
30
25
20
15
10
5
0
92% DIFFERENCE
0 1 2 3 4 5 6 7 8 9 10
TIME AFTER APPLICATION (MINUTES)

FIG. 15.

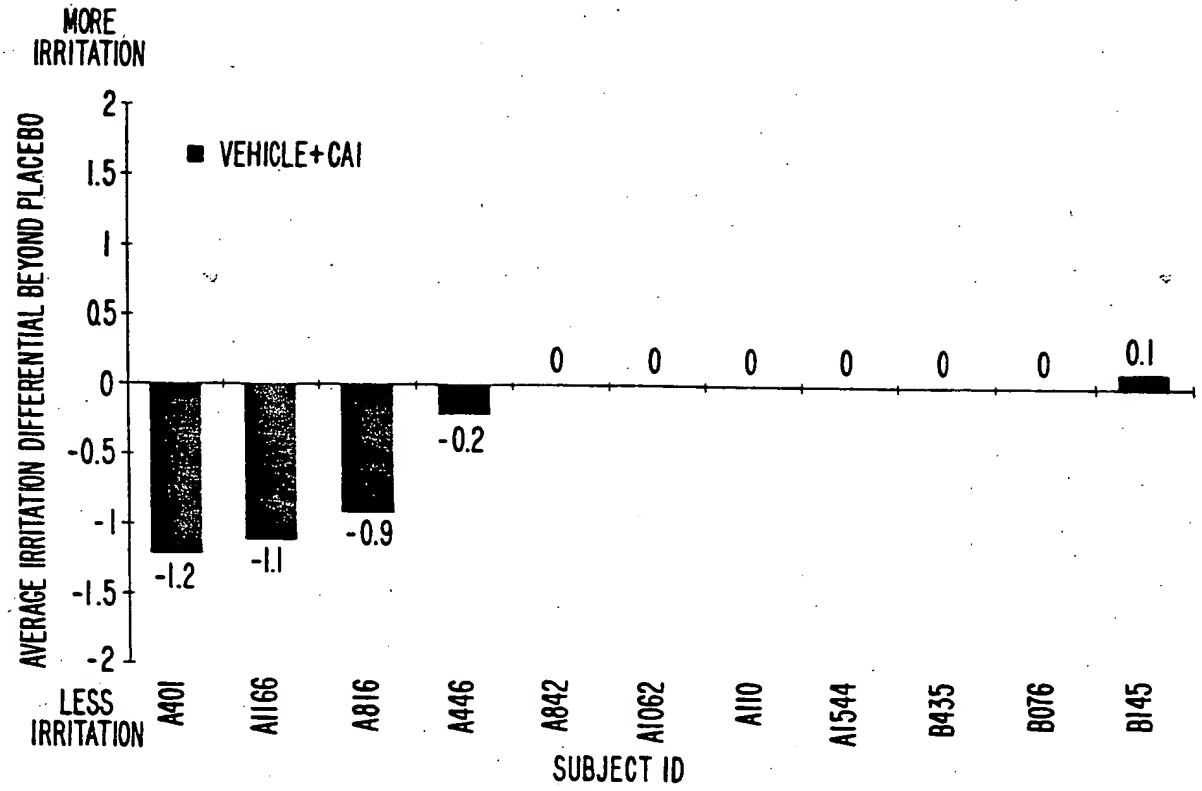

MORE IRRITATION
LESS IRRITATION
AVERAGE IRRITATION DIFFERENTIAL BEYOND PLACEBO
VEHICLE+CAI
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-1.2
-1.1
-0.9
-0.2
0
0
0
0
0
0
0.1
A401
A1166
A816
A446
A842
A1062
A110
A1544
B435
B076
B145
SUBJECT ID

FIG. 16.

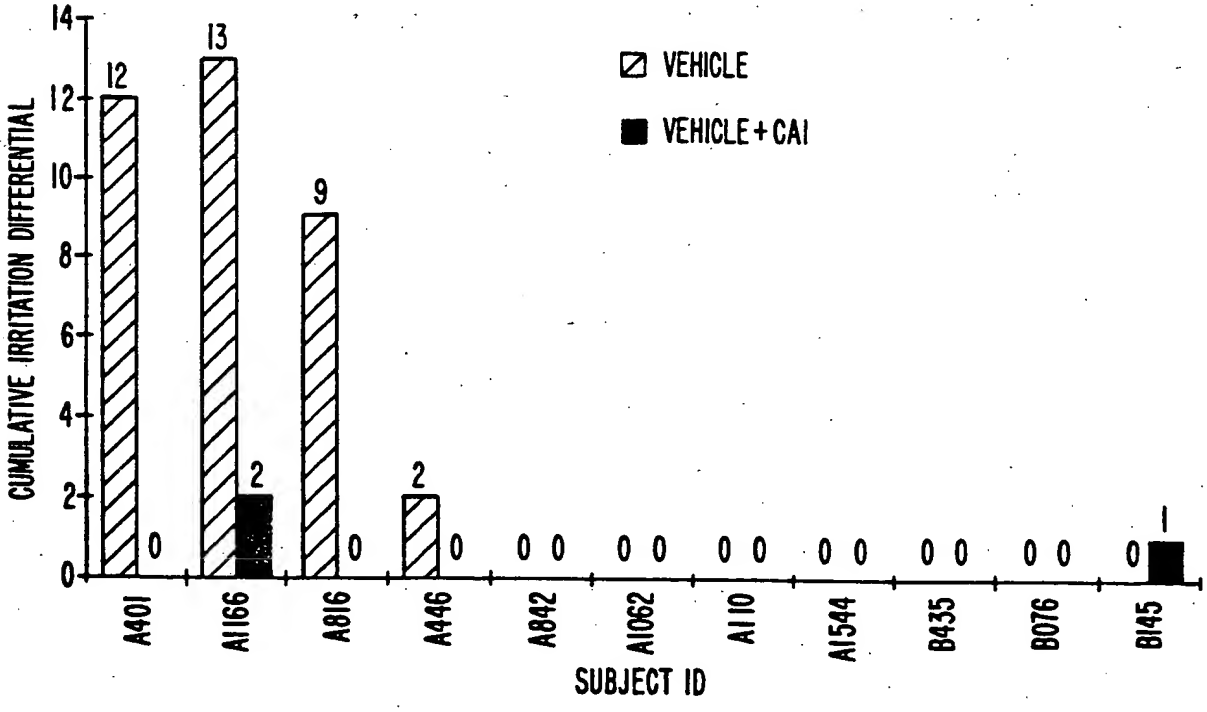

CUMULATIVE IRRITATION DIFFERENTIAL
VEHICLE
VEHICLE+CAI
14
12
10
8
6
4
2
0
12
0
13
2
9
0
2
0
0 0
0 0
0 0
0 0
0 0
0 0
1
A401
A1166
A816
A446
A842
A1062
A110
A1544
B435
B076
B145
SUBJECT ID

FIG. 17.

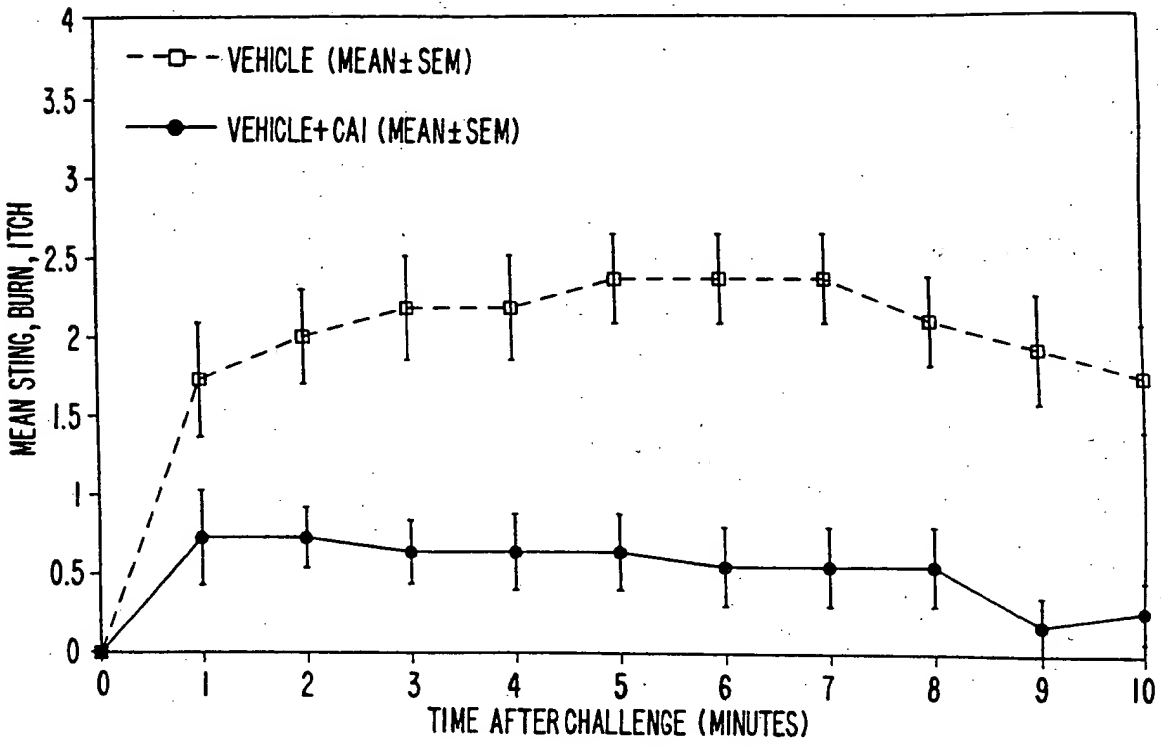

VEHICLE (MEAN± SEM)
VEHICLE+CAI (MEAN± SEM)
MEAN STING, BURN, ITCH
TIME AFTER CHALLENGE (MINUTES)
0
0.5
1
1.5
2
2.5
3
3.5
4
0
1
2
3
4
5
6
7
8
9
10

FIG. 18.

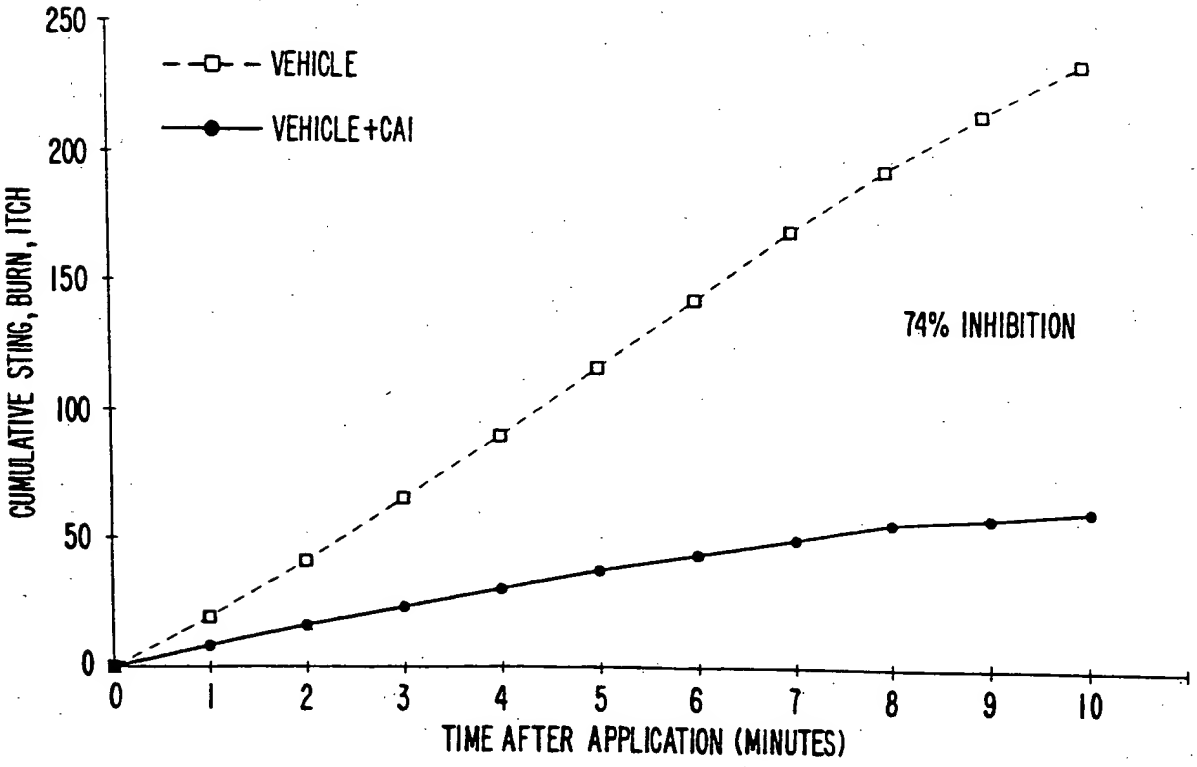

VEHICLE
VEHICLE+CAI
74% INHIBITION
CUMULATIVE STING, BURN, ITCH
TIME AFTER APPLICATION (MINUTES)
0
50
100
150
200
250
0
1
2
3
4
5
6
7
8
9
10

FIG. 19.

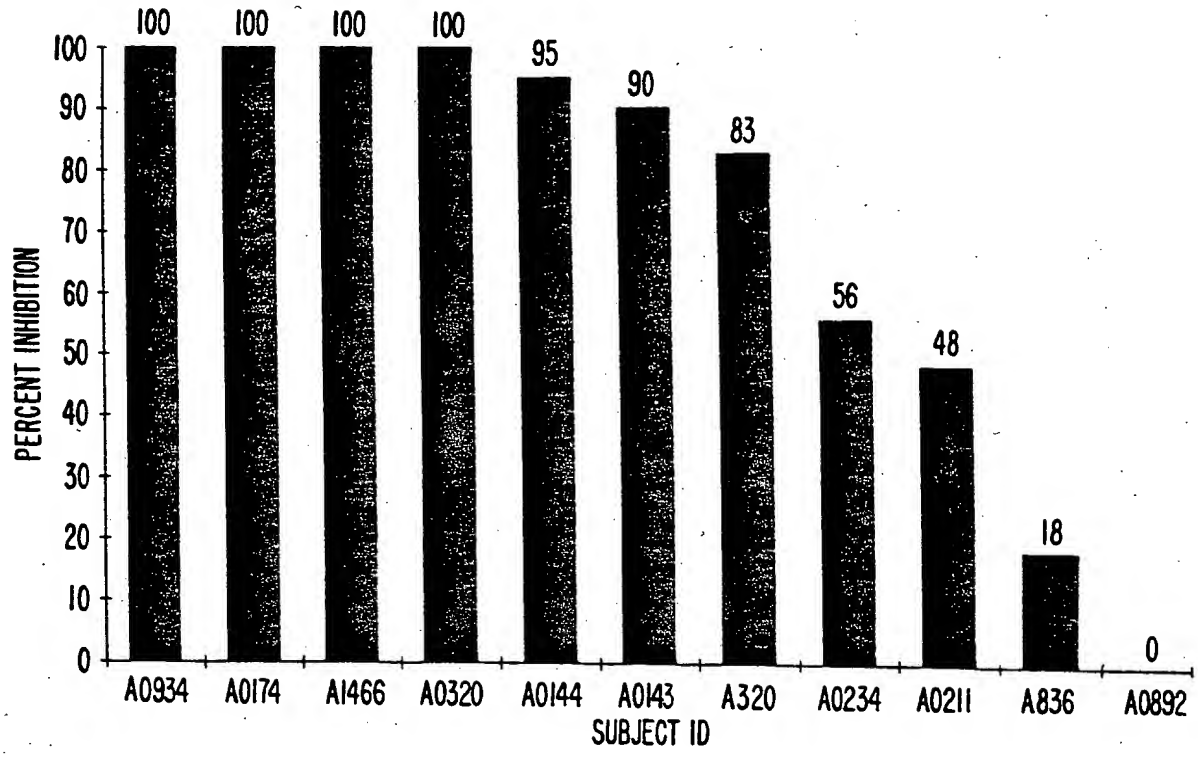

PERCENT INHIBITION
100
90
80
70
60
50
40
30
20
10
0
100
100
100
100
95
90
83
56
48
18
0
A0934
A0174
A1466
A0320
A0144
A0143
A320
A0234
A0211
A836
A0892
SUBJECT ID

FIG. 20.

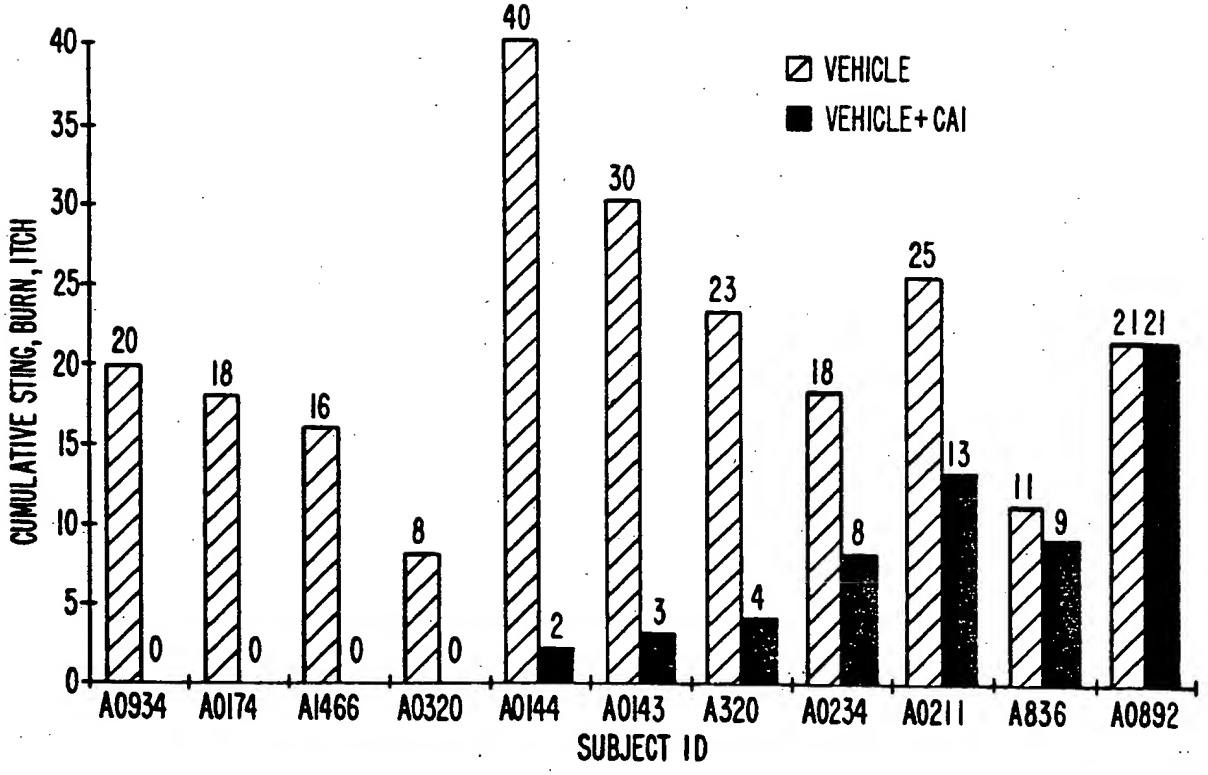

CUMULATIVE STING, BURN, ITCH
40
35
30
25
20
15
10
5
0
VEHICLE
VEHICLE+CAI
20
0
18
0
16
0
8
0
40
2
30
3
23
4
18
8
25
13
11
9
21
21
A0934
A0174
A1466
A0320
A0144
A0143
A320
A0234
A0211
A836
A0892
SUBJECT ID

FIG. 21.

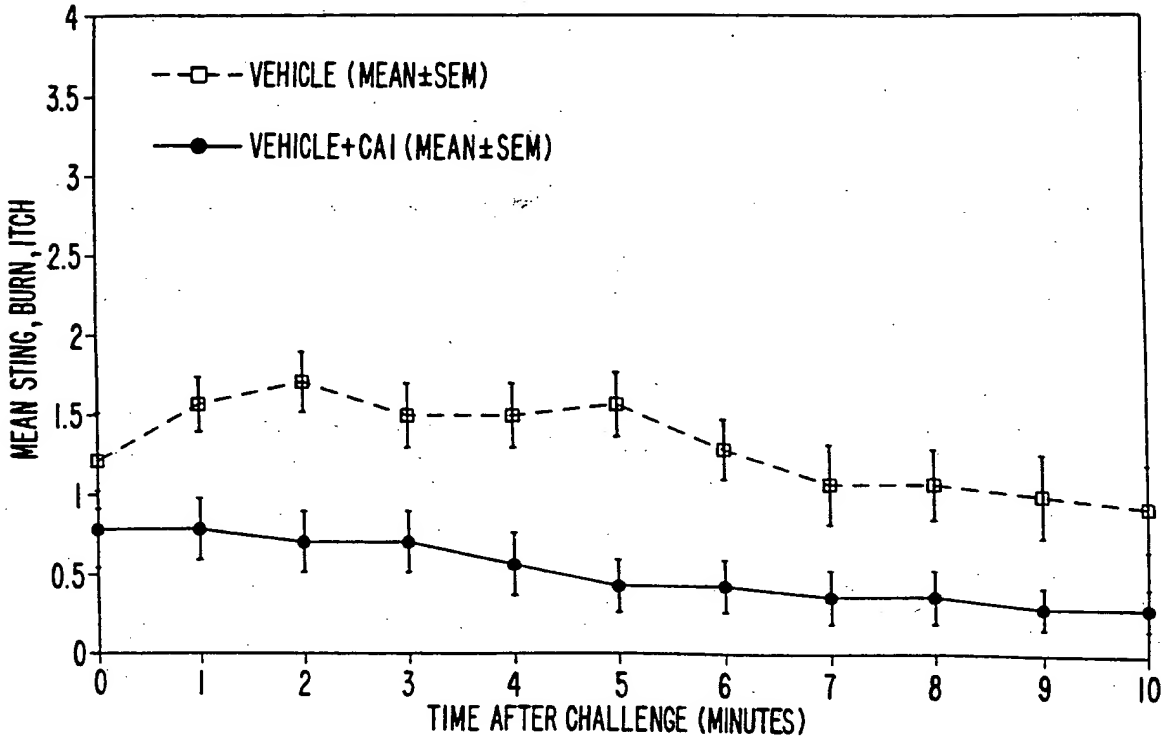
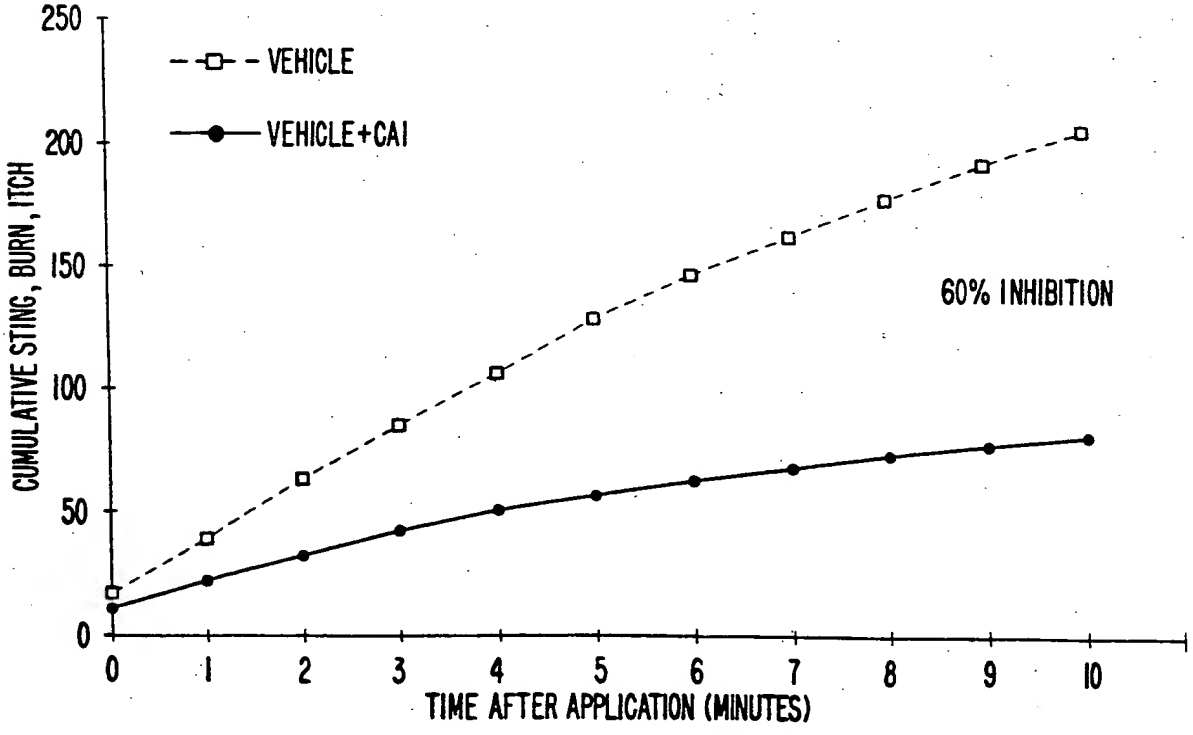

VEHICLE (MEAN±SEM)
VEHICLE+CAI (MEAN±SEM)
MEAN STING, BURN, ITCH
TIME AFTER CHALLENGE (MINUTES)
0
0.5
1
1.5
2
2.5
3
3.5
4
0
1
2
3
4
5
6
7
8
9
10

FIG. 22.


VEHICLE
VEHICLE+CAI
60% INHIBITION
CUMULATIVE STING, BURN, ITCH
TIME AFTER APPLICATION (MINUTES)
0
50
100
150
200
250
0
1
2
3
4
5
6
7
8
9
10

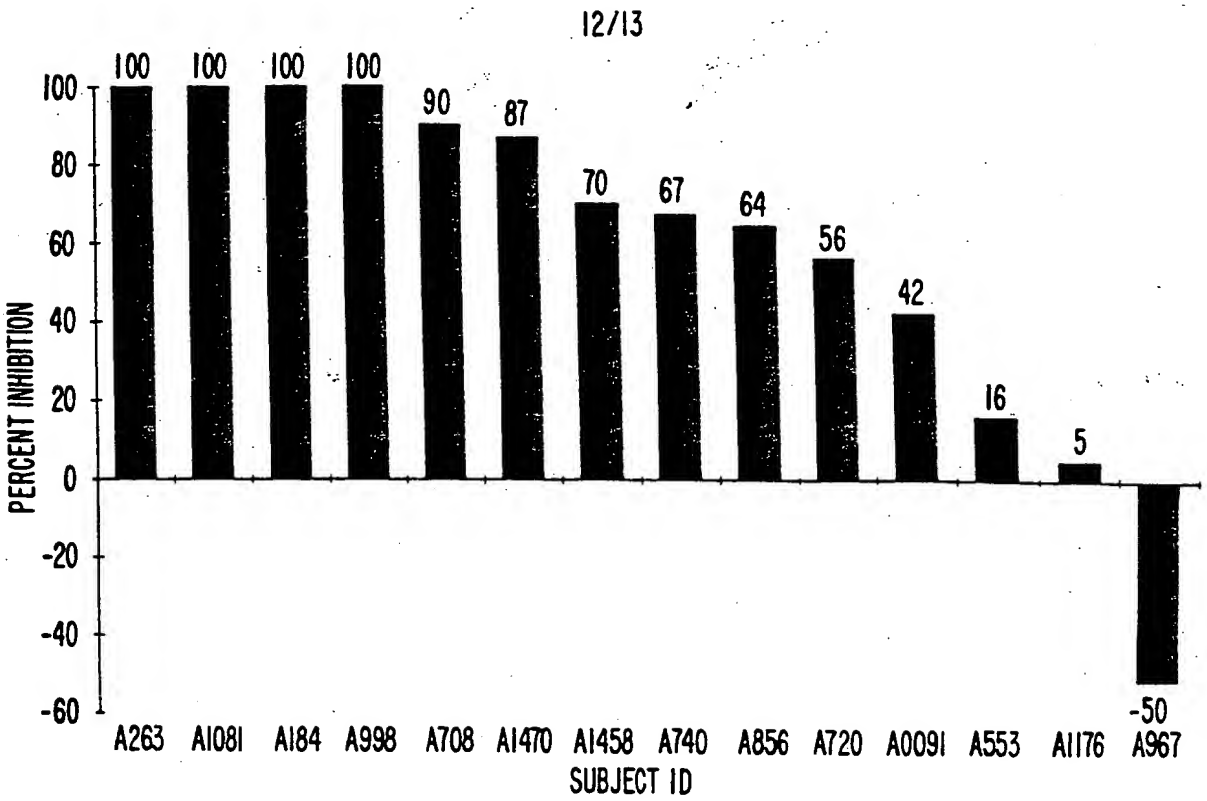

PERCENT INHIBITION
100
80
60
40
20
0
-20
-40
-60
100 100 100 100 90 87 70 67 64 56 42 16 5 -50
A263 AI08I AI84 A998 A708 AI470 AI458 A740 A856 A720 A0091 A553 AI176 A967
SUBJECT ID

FIG. 23.

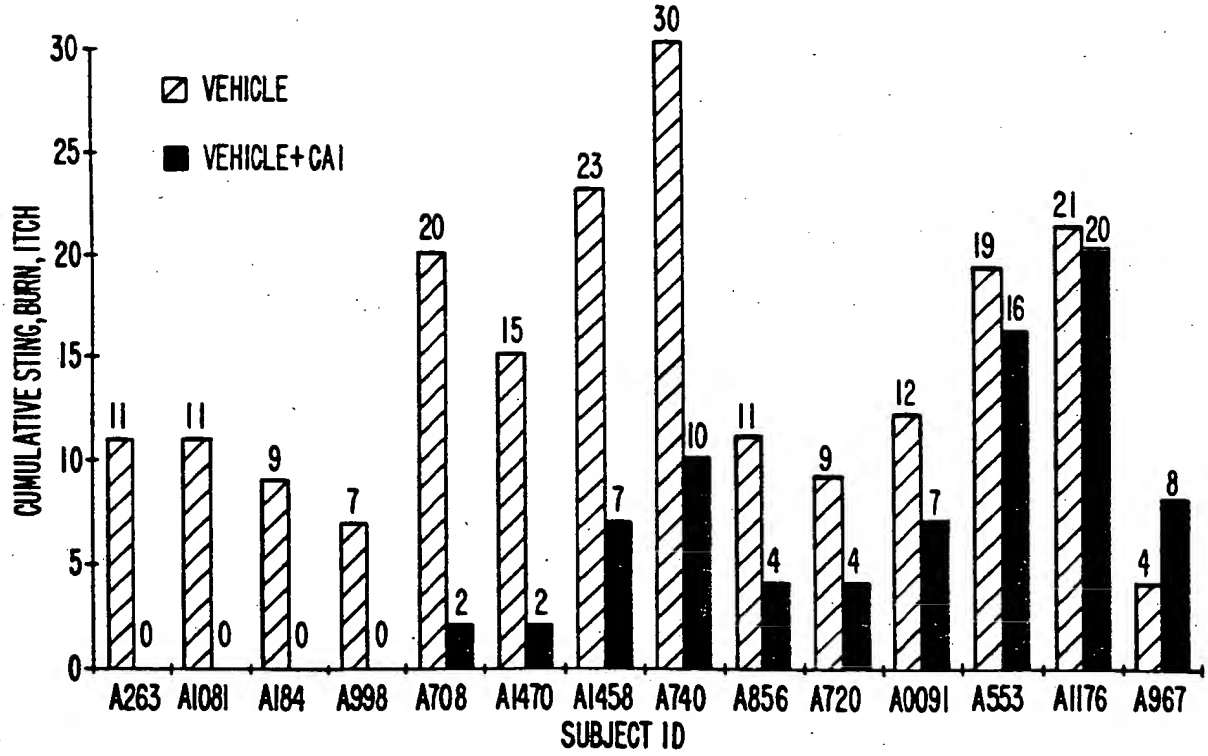

VEHICLE
VEHICLE+CAI
CUMULATIVE STING, BURN, ITCH
30
25
20
15
10
5
0
11 0 11 0 9 0 7 0 20 2 15 2 23 7 30 10 11 4 9 4 12 7 19 16 21 20 4 8
A263 AI08I AI84 A998 A708 AI470 AI458 A740 A856 A720 A0091 A553 AI176 A967
SUBJECT ID

FIG. 24.

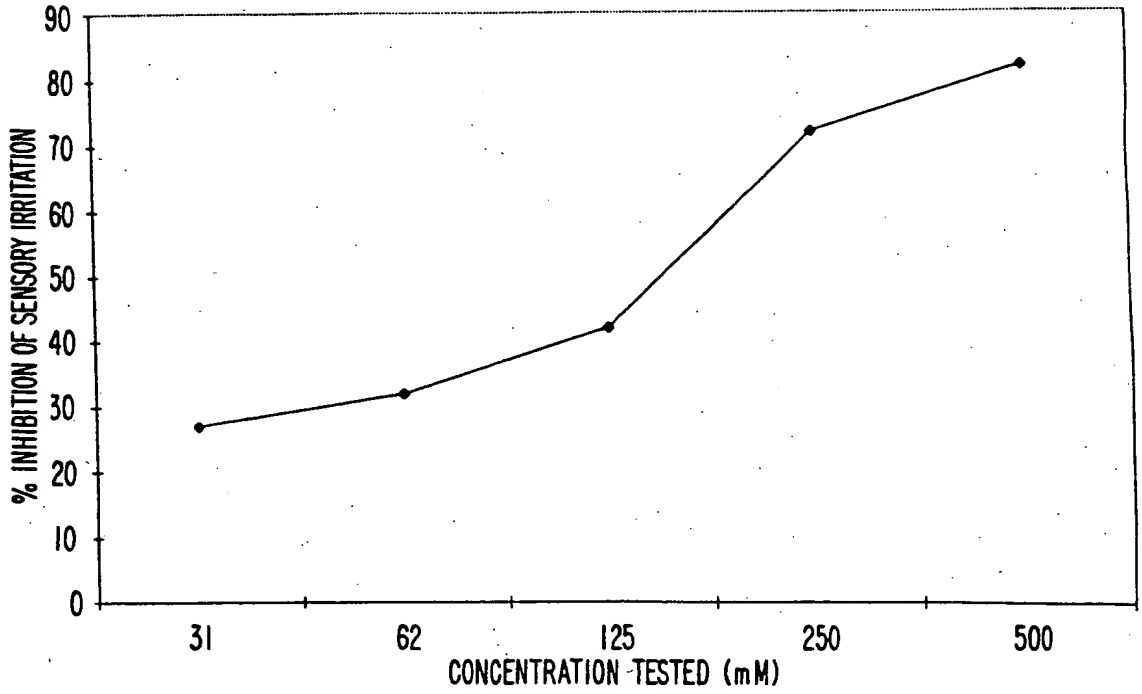

90
80
70
60
50
40
30
20
10
0
% INHIBITION OF SENSORY IRRITATION
31
62
125
250
500
CONCENTRATION TESTED (mM)

FIG. 25.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/16985

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 7/00
US CL :424/401

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/401

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,943,432 (BIENER) 24 July 1990, columns 1-6.	1-114
Y	US, A, 4,477,439 (D'ALELIO) 16 October 1984, columns 1-4.	1-114

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 APRIL 1996	03 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SALLY GARDNER Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*